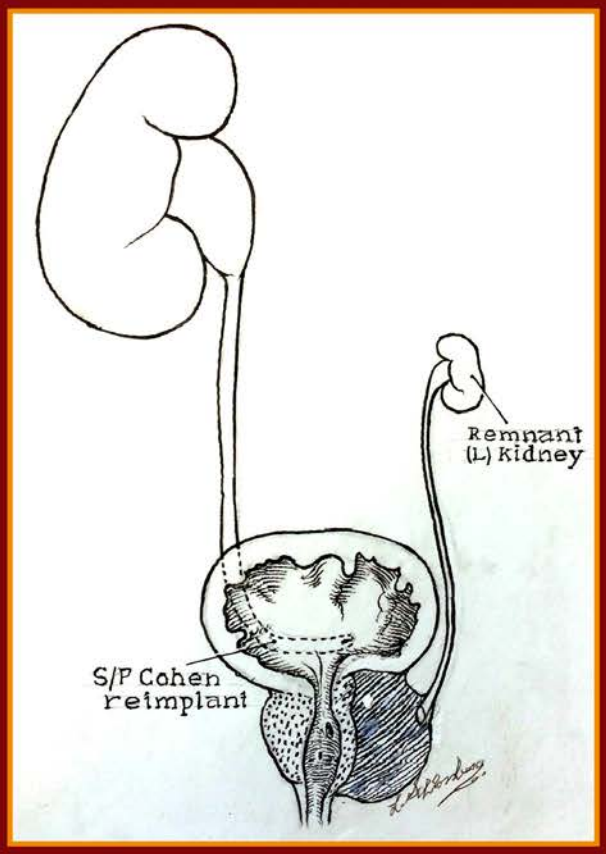
THE KELALIS-KING-BELMAN TEXTBOOK OF CLINICAL PEDIATRIC UROLOGY

SIXTH EDITION



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The Kelalis–King–Belman

Textbook of Clinical Pediatric Urology

Sixth Edition

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Textbook of Clinical Pediatric Urology

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Chapter 4: In-Office Ultrasonography	
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Preface

We are honored to again have the opportunity to edit the Sixth Edition of the "Kelalis, King and Belman," the standard text in Pediatric Urology for four decades. The title of the Fifth Edition was changed to *The Kelalis–King–Belman Textbook of Clinical Pediatric Urology* to commemorate the original editors. Our great friends and mentors Barry Belman and Lowell King were very helpful in orienting us to the prior edition. We are saddened at the loss since then of Dr. King, who with the late Panayotis Kelalis cannot see the current fruits of their original vision. We hope that the current text continues to build on that vision in ways that would make them proud.

The specialty of pediatric urology continues to change rapidly, and we hope that the new format of the text, with an emphasis on web-based resources, will reflect that. Much open surgery that was transitioned to laparoscopic or endoscopic surgery is now approached using the surgical robot. Availability of "big data" that crosses institutions, states and nations is allowing sophisticated health services researchers in our field to understand trends, identify risk factors, and provide advice for new pathways of care. This provides the potential to get the right care only to those who need it, increasing effectiveness and decreasing cost. Advances in understanding of hormone receptor signaling and urothelial-mesenchymal interactions are suggesting new forms of preventive therapy for developmental anomalies in the future. Emergence of population health thinking is forcing us to reconsider the ways that we evaluate and treat common conditions, such as urinary tract infection and prenatally detected hydronephrosis. In short, our field is beginning to look rather sophisticated.

We kept the general organization of the prior edition, starting with chapters of general interest, and then proceeding through each of the systems or anatomical areas of interest to urologists, and including chapters on basic science research to point the way to future clinical applications. New to this edition, and nearly unique in scope, we have added a video-based surgical atlas, edited by Joao Luiz Pippi Salle, which can be viewed as a stand-alone compendium or linked from the individual chapters. As in the prior edition, we are indebted to our returning authors and to our many new authors who have infused the text with their energetic contributions.

The text will again be accompanied by a study guide. We hope that this will prove helpful to urology and pediatric urology trainees, but also to all of us who need to prepare for certification or recertification examinations in Pediatric Urology—a subspecialty certification that was only in the planning stages when our last Edition was published. We would like to thank the authors and editors for contributing to these questions, which add significant effort above and beyond completing a chapter.

As always, this is intended as a reference work, but not necessarily the last word. We have tried to present controversy where it exists, but in the end all recommendations are made based on the experience and best belief of the authors. The authors have been chosen in every case for their expertise, experience and rationality. Although we, as editors, may not have agreed with everything our authors have stated, we consider each of them a master in their area, and have tried to minimize our influence on their message.

The change that has had the most profound impact on the Sixth Edition is the addition of a group of editors to the team who represent the best and brightest in Pediatric Urology. These are the individuals who worked directly with the authors, primarily edited the manuscripts, chased down the videos and assured appropriate formatting, and dealt with the many technical potholes that characterized this long journey. Our hats are off to Drs. Austin, Coplen, Copp, Herndon, Lorenzo, Merguerian, Ost, Park, Pohl, and Shukla, without whose efforts this book does not exist.

We are especially indebted to our publisher, Ms. Miranda Bromage of Taylor & Francis, who picked up the pieces of a technical disaster, and with the able help of Cherry Allen reassembled this complicated project from beginning to end to make it something better than it would have been in the first place. We also thank Kyle Meyer at CRC Press/Taylor & Francis and Nick Barber at Nova Techset for their professional work on this book.

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Douglas A. Canning
Antoine E. Khoury
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Editors

Dr. Steven G. Docimo, MD, MMM, earned his MD from the Johns Hopkins University School of Medicine, trained in general surgery and urology at Naval Hospital, Bethesda, Georgetown University, and the Harvard Program in Urology at the Brigham and Women's Hospital, and completed an AUA Scholars Research Fellowship in the Department of Urology at the Children's Hospital, Boston. He completed pediatric urology training at the Johns Hopkins School of Medicine, where he remained on faculty and was named Professor with Tenure. He was later chief of the Division of Pediatric Urology at the University of Pittsburgh School of Medicine for 11 years and founded the Pittsburgh pediatric urology fellowship program. He served as chief medical officer for the Children's Hospital of Pittsburgh of UPMC (University of Pittsburgh Medical Center), a position he held for more than 10 years, while also serving as vice president for Pediatric Subspecialty Services within the University of Pittsburgh Physicians, and President of Children's Community Pediatrics. He is currently senior vice president, Clinical Operations for National Relationships for the Children's Hospital of Philadelphia. He has authored more than 300 papers, abstracts, videos, books, and book chapters.

Douglas A. Canning, MD, is chief of the Division of Urology at Children's Hospital of Philadelphia and a professor of urology in surgery at the Perelman School of Medicine at the University of Pennsylvania. He holds the Leonard and Madlyn Abramson endowed chair in pediatric urology.

Dr. Canning earned his medical degree from Dartmouth Medical School. He completed his general urological residency training at the National Naval Medical Center in Bethesda, Maryland. He then completed his pediatric urological fellowship training at The James B. Brady Urological Institute at the Johns Hopkins Hospital. Following a four-year military tour during which he was director of pediatric urology at the Naval Medical Center, San Diego, he returned to the east coast and joined the urology staff at CHOP in 1992. In 1997, Dr. Canning was appointed director of the Division of Urology at CHOP. Shortly after his appointment, he was named to the Leonard and Madlyn Abramson chair in pediatric urologic research.

He is author or coauthor of more than 100 peer-reviewed publications, three textbooks, and more than 500 editorials in urology. He is a member of the Urological Survey Editorial Committee for the *Journal of Urology*. He is an internationally recognized expert in all areas of pediatric reconstructive urology with a particular interest in the care of children with complex urological conditions such as bladder and cloacal exstrophy, hypospadias, posterior urethral valves and genital anomalies in both sexes.

Dr. Antoine Khoury, MD, FRCSC, FAAP, is the chief of pediatric urology and, with more than 25 years of experience, leads the CHOC (Community Housing Opportunities Corporation) Children's Urology Center. He is a professor of urology at University of California, Irvine (UCI) and the Walter R. Schmid endowed chair in pediatric urology at UCI.

Dr. Khoury completed his residency training at the University of Toronto and did his fellowship training in pediatric urology at The Hospital for Sick Children in Toronto, under Dr. B. Churchill. Dr. Khoury has also spent time at the University of Calgary carrying out research in infection and biomaterials. His work there resulted in several publications and a patent award on the bioelectric mechanism to eliminate bacterial biofilms. He then joined the faculty of the division of urology at the Hospital for Sick Children in Toronto and was the division head from 1995 to 2008 before coming to CHOC Children's Urology Center.

Dr. Khoury has published more than 200 peer-reviewed publications and 60 book chapters. He has delivered over 160 lectures as a visiting professor or invited speaker at both international and national levels.

Dr. Joao Luiz Pippi Salle is the division chief of urology at Sidra Medical and Research Center in Doha, Qatar. He was the former chief of urology of the Montreal Children's Hospital as well as at the Toronto Sick Kids Hospital, in Canada. He was the inaugural chair of urology and regenerative medicine at Sick Kids Hospital, University of Toronto. Dr. Pippi Salle is a pediatric urologist with special interest in genito-urinary reconstruction. He is an innovative surgeon who developed new techniques for the correction of urinary incontinence, differences of sex development, exstrophy/epispadias complex, and hypospadias. He published numerous papers and book chapters and has been a visiting professor in 35 countries. He is dedicated to teaching having completed the Education Scholarship Program and served as the director of Continued Medical Education in the Department of Surgery at the University of Toronto. Dr. Pippi Salle is also committed to International teaching in several countries where he developed several successful workshops in reconstructive pediatric urology.

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Section 1

Evaluation of the Pediatric Urologic Patient

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CHAPTER 1

History and Physical Examination of the Child

Anton Wintner and T. Ernesto Figueroa

HISTORY

General Considerations

The path to caring for a patient and offering a solution to a medical condition begins with a thorough medical history, and subsequent physical examination. These are the most basic elements in medical care, and when properly conducted, they allow for understanding and appreciation of the medical condition, and the ability to initiate appropriate care for the patient. The extensive progress in medical technology has given the physician new tools for the diagnosis and treatment of most medical conditions; however, no technological advance can replace the sympathetic and discriminating ear of the physician, or the gentle and perceptive hand during the physical examination. In the diagnostic process, history accounts for 80% of the information, physical examination for 15%, and special investigations for 5%.[1] A thorough history is clearly the most enlightening component of the diagnostic process.[2]

The field of pediatrics is a rather unique branch of medicine in that the medical history is usually obtained from a person other than the patient, this being the mother, the father, other relatives, or a foster parent.[3] It is important to identify the person giving the history, and to clarify the relationship to the patient. As the physician first encounters the child and the parent, it is essential to introduce oneself and offer one's services to the patient and the family. In the complex environment of modern healthcare, the family is likely to come into contact with several members of the medical team besides the pediatric urologist that they are there to see, and it can be rather confusing for the family to identify the role of each member. Many medical organizations have promoted the concept of Acknowledge–Introduce–Duration–Education–Thank you (AIDET) to encourage healthcare providers to clarify their role in the service line of the patient.[4] The accompanying adult should be asked about his or her relationship to the patient. In order to protect the patient's confidentiality and privacy, physicians have the professional obligation to define the relationship of the accompanying adult to the patient, and to determine who will be the recipient of the medical information related to the pediatric patient.[5] Current federal regulations establish limitations on the medical information that can be shared with individuals other than the patient, and there can be serious penalties for ignoring this federal directive.[6] The physician should not assume that the accompanying adult has legal custody of the child.

Upon approaching an examination room, it is important to remember that small children will often move about the room, as the family waits for the physician. Prior to entering the room, the physician should first knock gently on the door to alert the parents to pick up the child who could be sitting behind the door, and then open the door cautiously. When first encountering the child and accompanying adult, and after introducing oneself to the patient and family, it is helpful to ask what the child likes to be called, and address the child in that manner. Also, it is beneficial to find an area of interest that will show patients that we care and are interested in them, such as asking what type of play they enjoy, offering supportive commentary about their clothes, or inquiring about their interests in sports or other activities. The child should feel that they are the primary interest of the interaction, and regardless of the age, the physician should look at the child and talk to him or her in words that the child can understand at various times during the encounter. A soft and courteous tone of voice and a sympathetic look are essential in developing a trusting relationship with the child, assuring the patient and the family that the physician is concerned with his or her condition. Abrupt, pressing, and hurried interfaces often have a profoundly negative effect on the initial, and subsequent, patient–physician interactions. The physician should convey a willingness to listen, and demonstrate empathetic understanding for the information being gathered.[2] If a young child is not receptive to the interaction and is disruptive during the history taking, it is helpful to seek distraction techniques, such as a toy box, coloring books, formula or snacks, or removal from the examination room, to allow adequate history gathering. A comfortable environment can enhance communication.[3] In essence, it is important to convey to the parent the interest in the child as well as the illness.[7]

History of Present Illness

The pediatric urologic history should be tailored to the condition of the patient. Some conditions are immediately evident, such as the healthy newborn with hypospadias or undescended testis, and these require a more focused and limited approach to the history. Other conditions, such as combined diurnal and nocturnal enuresis in an older patient, are likely to require a more detailed and comprehensive assessment of the medical history. Thus, not every patient seen by a pediatric urologist will require an extensive medical history with a need to cover all the items traditionally listed in the medical history of a child. However,

the role of the pediatric urologist is to determine what key questions are necessary to formulate the most accurate description of the patient's genitourinary condition.

A good approach to history taking is to begin by asking broad-based, open-ended questions in order to ascertain the chief complaint—the main reason why the patient is in the office—in the patient's (or parent's) own words. A simple option is to begin by asking, "What brings you in today?" or "How can I help you?" This is crucial because if the patient's chief complaint is not addressed, no matter how trivial it may seem or how great the care the physician provides otherwise, the patient (and parents) will not be satisfied. For example, an adolescent patient with mild hypospadias may be more concerned with the appearance of excessive dorsal foreskin than the location of the meatus. Once a clear chief complaint is established, the physician may narrow his or her questioning to keep the patient focused and gather specific details. The patient and family should always be questioned about possible associated genitourinary symptoms, including flank pain, abdominal pain, dysuria, hematuria, incontinence, frequency and urgency, difficulty with urination, previous urologic surgery, and scrotal pain and swelling. Other symptoms, such as malaise, fever, weight loss, constipation, vomiting, or body posturing, should be reviewed as part of the history of present illness (HPI) when they are pertinent to the differential diagnosis.

Age-Related Considerations

In the evaluation of children, certain age-related, well-recognized behavioral characteristics affect how children respond to the interaction with a physician or other healthcare providers. There is an ample bibliography on this topic in the pediatric and psychological literature, but for the purposes of this chapter, the following outline of age competencies[8] can be useful to the pediatric urological care provider:

1. Infants (birth to 1 year)
   a. Characteristics
      i. Parents or primary caregivers are most important.
      ii. Sense of trust and security develop.
      iii. Fear of the unfamiliar. Stranger anxiety evident at 6–8 months.
      iv. Major source of pleasure is oral activities, such as sucking, biting, and chewing.
      v. Learns by imitation and repetition.
2. Toddlers (1–4 years)
   a. Guidelines
      i. Allow choices if possible. Prepare before a procedure.
      ii. Give one direction at a time.
   b. Characteristics
      i. Asserts independence and develops a sense of will. Has temper tantrums.
      ii. Fear of separation between 2 and 2½ years.
      iii. Learns cause and effect.
      iv. Discovers ability to explore and manipulate environment.
      v. Constructs three- to four-word sentences.
      vi. Short attention span.
3. Preschoolers (4–6 years)
   a. Guidelines
      i. Offer badge of courage (stickers) and praise.
      ii. Use dolls or puppets for explanation when performing procedures and involve child when possible.
   b. Characteristics
      i. Fears include bodily injury and mutilation, castration (males), and the dark.
      ii. Physically aggressive.
      iii. Masters and acquires new skills.
      iv. Major skill is conversation.
      v. Speaks in eight-word sentences by age 5.
      vi. Understands numbers and can count.
      vii. Questions why.
4. School age (6–12 years)
   a. Guidelines
      i. Provide privacy and explain procedures in advance using correct terminology.
      ii. Clearly define and reinforce behavior limits.
   b. Characteristics
      i. Important to belong and gain approval of peer group.
      ii. Rule-bound.
      iii. Greatest fear is loss of control.
      iv. Distinguishes between right and left side at age 7.
      v. Develops personal standards of right and wrong at age 9.
      vi. Play, simple instruction, repetition, books, visual aids, and examples are ways that an 8-year-old learns.
5. Adolescents (13–17 years)
   a. Guidelines
      i. Provide privacy and allow maintaining control.
      ii. Involve them in decision making and care.
      iii. Present them with their "rights."
      iv. Discuss virginity, prevention of sexually transmitted diseases, and pregnancy.
   b. Characteristics
      i. Development of identity.
      ii. Rapid growth of skeletal muscle mass, adipose tissue, and skin.
      iii. Common fears include loss of control, not being accepted by peers, and separation from peers.
      iv. Think they are invincible and bad things will not happen to them.
      v. May criticize parents.
      vi. Identity is threatened by hospitalization, and they are concerned with bodily changes and appearance.

Privacy and Confidentiality of the Adolescent Patient

Adolescence is a time of rapid and significant physical, emotional, and psychological change. Although the adolescent patient may represent a challenging patient for the pediatric urologist, this encounter also represents an opportunity for the urologist to educate the patient about the bodily changes (puberty), as well as about

sexuality, safe sexual practices, and sexually transmitted diseases. Many adolescents are reserved about their medical conditions, and as a group, they tend to place a greater value on peer relationships than parental or adult relationships. Gathering information from adolescents is particularly challenging, and many will not seek medical care for fear of anticipated shame and embarrassment, loss of autonomy, and fear of not being understood.[9] When facing an adolescent patient, part of the history should be obtained in the presence of a parent or guardian, but the patient should also be queried about urinary symptoms and sexual matters in a private setting. The transition from the history-gathering portion of the medical encounter to the physical examination is a good opportunity to isolate the adolescent patient from the parent to obtain additional pertinent information. Prior to proceeding with the examination, the adolescent patient should be asked if he or she prefers a private room or the presence of a parent or chaperone during the exam. Legally, minors cannot consent to medical care, so the request to examine the patient should be made in the presence of the parent. Any information obtained during this interaction should be considered confidential. There are federal guidelines regarding the confidentiality and privacy of medical information of minors, although there is variation of guidelines and privacy laws of minors from state to state.[10,11] Any healthcare provider caring for adolescent patients is encouraged to become familiar with the local (county or hospital), state, and federal guidelines regarding the privacy and confidentiality of minors, and should not hesitate to involve social services when the information poses legal and ethical ambivalence.

Past Medical History

A thorough past medical history is vital for the care of the pediatric patient. Since the history often cannot be directly solicited from the young patient, history previously recorded by another physician may be incomplete or contain inaccuracies. As such, the family should be allowed adequate opportunity to communicate their perspective of the course of events that have transpired in the life of the child. The accuracy of the past medical history is crucial because many pediatric conditions are age dependent, and therefore the physician's suspicion (and consequently the condition's position on the differential diagnosis) may depend on the age at which a particular complaint began.

The past medical history should include as much information as possible about previous hospital and emergency room visits. The patient and family should be asked about all the diagnoses that the child carries, at what age they were diagnosed, and how each diagnosis came about. Any procedures or surgeries that the child has undergone, as well as their timing, should be recorded.

The physician should ensure that the surgical history is concordant with physical exam findings, such as scars, as there is large variability among families in the degree of sophistication of their medical knowledge. This is even more important if future surgery is a possibility, and if any uncertainty arises, the previous surgeon should be consulted.

The urologist should keep in mind that many nonurological conditions may have urologic sequelae, and thus a complete understanding of the child's medical history is imperative. For example, a child may present to the urologist with new-onset hematuria, and assessment may show that the child had gastrointestinal symptoms of vomiting and diarrhea before progressing to hematuria, suggesting the possibility of hemolytic uremic syndrome. Moreover, many conditions that are not typically treated by the urologist may affect the urogenital tract, and thus may be first diagnosed by the urologist. As an example, scrotal pain and swelling may be the initial presentation of Henoch–Schönlein purpura.[12]

Prenatal History

The past medical history should include information about the prenatal history and pregnancy. The urogenital tract is the most common location for congenital malformations, many of which may be directly identified by prenatal screening. Examples include conditions such as hydronephrosis, multicystic dysplastic kidney, unilateral renal agenesis, bladder exstrophy, prune belly syndrome, posterior urethral valve, and spina bifida. Other urological conditions may be indirectly diagnosed. For example, imperforate anus (with its urological sequelae) may present with bowel calcifications on prenatal ultrasound. Still other conditions, such as congenital heart disease and Down's syndrome, may be diagnosed prenatally, raising suspicion for the urologic conditions with which they are commonly associated.

The prenatal history should also include any illness or medications to which the mother was exposed during pregnancy. Viruses and medications (both prescription and nonprescription drugs) may be teratogenic, providing insight into the etiology of some congenital anomalies.

The child's gestational age at birth should also be noted, as premature children tend to have a more complex medical history than full-term infants. Lung immaturity is also much more common in premature infants and may impact the way the child's responds to anesthesia.

Review of Systems

The review of systems (ROS) is an opportunity for the physician to ask questions about symptoms that the patient may not consider to be important, or even related to the main complaint. Yet often these symptoms are both important and related, and provide invaluable insight into the patient's condition. The ROS may also serve to ensure that the physician has not overlooked any symptoms the patient may be experiencing. The comprehensiveness of a formal ROS varies from physician to physician, but the key is to ensure that it is completed in as consistent of a manner as possible.

The ROS should begin with a few general questions about the growth and development of the child. A comprehensive developmental history is not crucial, although a general awareness about the patient's ability to reach developmental milestones is important.

Next, broad questions about heart conditions, heart murmurs, visits to cardiologists, and any pulmonary conditions, such as asthma, will help give insight into the patient's risk factors for general anesthesia.

Questions about the gastrointestinal tract are often pertinent to the urologist. Particularly in children, poor defecation habits and constipation have long been recognized to contribute to a number of urological conditions, from urinary tract infections to voiding symptoms and urinary incontinence.[13,14] The term *constipation* implies various meanings to patients and healthcare providers, and it is beneficial to define what we mean by the term *constipation*, including hard and painful defecation, and infrequent defecation of less than three bowel movements per week.[15]

General questions about the genitourinary tract and voiding should be asked of all patients presenting to the urologist, even if these questions are not directly related to the patient's chief complaint. The patient and family should be questioned about previous kidney problems, and pain in the area of the low back. The patient's voiding history should be taken, and the patient and family asked about symptoms of frequency, urgency, day and night incontinence, dysuria, and hematuria. Young male patients in particular should be questioned about their urinary stream. A double stream may indicate an accessory urethra or urethrocutaneous fistula, while a high-pressure, deflected stream with prolonged voiding time is characteristic of meatal stenosis.

Review of the neurological history of the patient should include questions about seizure history, as most first-time seizures occur in childhood. The child and family should also be questioned about dizziness and fainting, as well as any numbness, weakness, or difficulty running or playing.

Finally, the physician should screen the child for symptoms of depression and anxiety. The time around puberty is especially stressful, and this stress may be compounded in children with urological abnormalities or medical conditions in general. Children who are depressed or suffering from severe anxiety should be appropriately referred. Failure to address psychiatric concerns will likely lead to worse medical outcomes, as depressed patients are less likely to be compliant with treatment.[16]

Medications

Any previous or current medications should be documented. The physician should also note the reason for each medication, the dosage, the typical schedule, how long the child has been taking the medication, and any recent changes. The patient and family should also be asked in a delicate manner about the degree of compliance to each medicine, and whether they perceive it to be effective.

The physician should consider the possible interactions and side effects of the patient's current medications and any new medicines to be prescribed. Many medications have cholinergic or anticholinergic properties, which may affect voiding and urinary function. Particularly in children, the physician should carefully weigh the pros and cons of beginning any new medications and discuss these with the family.

In order to reduce the occurrence of medication errors and patient harm, the Joint Commission introduced the concept of "medication reconciliation" in 2006.[17] When admitting a patient to the hospital, their medication regimen should be carefully reconciled to avoid duplications and omissions. Abrupt or accidental changes in medication may not only confuse the clinical picture but also cause direct harm to the child through overdose or withdrawal. Upon discharge, the patient's preadmission medication regimen should be carefully reviewed, as some medications may have been stopped or altered at the time of admission. It is the responsibility of the discharging physician to ensure that all preadmission medications are restarted at the time of discharge, if required.

Allergies

One of the greatest dangers in starting a new medication is an allergic reaction, which in the worst case may be anaphylactic. This may be avoided in most cases with a careful allergy history, as initial exposure to a medication rarely results in life-threatening anaphylaxis. Typically, life-threatening anaphylaxis follows immune system sensitization to a particular antigen, often accompanied by an initial mild reaction. However, many children have no prior documented history of exposure, and can progress to anaphylaxis and a risk of dying from the event.[18] Patients and their family should be asked about which medicines they are allergic to, what type of reaction they have, and when they were last exposed. Patients should also be asked about nonmedicine allergies, such as shellfish and latex. Seasonal allergies rarely have direct crossover with medications, although children with seasonal allergies may be more prone to reactive airway disease. The family should be questioned about other members having allergies to medications, specifically antibiotics and penicillin.

Most young children have had little exposure to medications, and it may be that their first allergic reaction results from antibiotics used to treat or prevent a urinary tract infection. Newborn children with known urinary tract abnormalities are often placed on antibiotic prophylaxis in the first few days of life as their first medication.[19] The risk of anaphylaxis with penicillin has been estimated at 0.015%, with a fatality rate of 0.002%.[20] If a reaction does occur, the pediatric urologist or pediatrician should immediately stop the medication and document the reaction. Signs of respiratory compromise or anaphylaxis mandate emergency treatment.

Subacute Bacterial Endocarditis

Genitourinary surgery was, in the past, one of the common indications for subacute bacterial endocarditis (SBE) prophylaxis in patients with some types of congenital heart disease.

According to the 2007 American Heart Association guidelines, however, "antibiotic prophylaxis solely to prevent infective endocarditis is no longer recommended for patients who undergo a gastrointestinal or genitourinary tract procedure, including patients with the highest risk of adverse outcomes due to infective endocarditis."[21]

Despite these recommendations, the urologist may be well served to have a conversation with the child's cardiologist about the need for SBE prophylaxis, as some cardiologists may not be completely comfortable with this approach.

Family History

The importance of a detailed family history must be emphasized. Pediatric patients are young, and therefore have had much more limited environmental exposure than older individuals. This greatly increases the likelihood that a given disease has a genetic component. Examples of genetic disorders include autosomal recessive polycystic kidney disease, von Hippel–Lindau disease, and renal tubular acidosis. Even diseases that are not strictly heritable, or in which no specific genetic mutation has been identified, may have a familial tendency. Examples of such diseases include vesicoureteral reflux, urinary tract infections, voiding disorders, and hypospadias.

Gathering of the family and genetic history for urologic conditions may prove challenging for several reasons. First, many genetic disorders have incomplete penetrance, making affected individuals harder to identify. For example, a patient with moderate hypospadias may have an affected grandfather who was never diagnosed because the grandfather's hypospadias was mild and did not cause the grandfather concern. Second, urologic conditions, particularly genital disorders, are often not openly discussed, making it more difficult to identify affected relatives.

Social History

Sexual History

A sexual history should be gathered in all adolescent and preadolescent patients. The history should always be taken in a quiet, private place where the patient will be more likely to answer questions openly and honestly. A carefully presented, nonjudgmental assessment of sexual history should be part of the medical history of every pubertal patient. It is essential that the patient is allowed all latitude to feel comfortable in discussing this most personal aspect of their medical history. An introductory description from the physician explaining that this is an integral part of medical care, and that all patients go through this evaluation, may help alleviate the expected apprehension from the patient.[22]

Patients should be asked about their sexual habits (number of partners, use of contraceptives, etc.) and should be appropriately counseled about safe sex practices. Furthermore, patients should also be questioned about symptoms of sexually transmitted infection so that they may be treated appropriately if required. Patients should be asked about genital itching, sores, discharge, dyspareunia, and previous history of sexually transmitted infection. The urologist should always keep in mind that many patients with complex medical conditions, such as spina bifida, may not have the peer support groups and educational opportunities of the rest of the healthy population, and these encounters with the healthcare provider are unique opportunities to offer teaching and answers to the silent questions that many of these patients have about sexuality.[23]

Substance Use

Both the family and the child should be questioned about substance use. Most studies show that patients who are addicted to tobacco and alcohol become addicted before adulthood. Tobacco and alcohol may lead to marijuana and other drug use in adolescence and later life, and have significant morbidity in and of themselves.[24] Patients should be counseled about these dangers and offered resources for quitting if required.

Families should also be questioned about adult substance use in the home. This must be done in a gentle, nonaccusatory manner. Risks such as secondhand smoke, which are obvious to the physician, may not be obvious to some parents. If the parents express interest in quitting an addictive substance, they too should be appropriately referred.

Environmental Exposure

Families should be asked about parental vocations and living situations, as certain industrial chemicals carry health risks to both the parents and child. If these risks can be identified early on, a strategy to mitigate them may be devised. There is mounting evidence on the effect of environmental agents on the incidence of hypospadias and cryptorchidism.[25]

School and Home

As part of the social history, the child should be asked about school and his or her social environment. Does the child have friends at school? Is he or she progressing well in his or her academics or struggling to pass the current grade? Has he or she been held back a year? Asking about school not only helps build a therapeutic alliance with the child and family, but also provides insight into social and mental development.

If not already obtained during the initial interaction, an assessment of the social history should include the marital status of the parents; who cares for the children if the mother is employed; number of siblings; progress at school; recent stressful experiences, such as moving or loss of a family member; and the type of interactions with other children (play dates, sports teams, etc.). Sometimes this information may elicit a diagnostic path possibly unrelated to the initial complaint of the patient.

Medical Insurance

Children without appropriate insurance coverage should not be turned away. Many states have social programs that cover children, particularly from low-income families. If a child does not have insurance, the family should be referred to a hospital case manager or other such worker who can aid them in attaining appropriate coverage.

PHYSICAL EXAM

Approach to the Examination of the Pediatric Patient

An important component of the physical examination of the pediatric patient occurs while obtaining the medical history and observing the patients and their relationship with their family. While listening to the family, the physician can assess the level of comfort of the child and his or her overall physical health, and anticipate the approach to the physical examination. Certain behaviors, of which the child may not even be aware, may become evident during this short observation period. These behaviors can provide the physician with invaluable insight into the etiology of the chief complaint. For example, the characteristic posturing of a child, Vincent's curtsy, may point to a child's attempt to temporarily prevent incontinence due to an inability to inhibit bladder contraction[26] (Figures 1.1 and 1.2).

When the time comes for the examination, the child should be informed in simple terms that are understandable to him or her that an examination is to take place. With younger children, having the parents stand or sit next to them during the examination can help reduce the fear of the experience. Young children, less than 1 year of age, can occasionally be examined while they recline in their mother's lap. Every effort should be taken to minimize separation anxiety in these children, common in children younger than 3 years of age. Preschoolers, ages 4–6 years, fear the possibility of bodily injury and mutilation, possibly castration, so the genital examination usually produces significant anxiety in this age group. In older children, and adolescents, privacy is very important, and respecting that privacy during the examination is vital, by asking the family members to look aside or to step out of the room. Examination of the adolescent should always be handled with sensitivity to avoid unnecessary embarrassment and preserve the dignity of the patient.[27]

Prior to placing hands on the patient, the examining physician should wash his or her hands, and repeat the hygiene practice at the end of the examination. A cold pair of hands can tense the patient unexpectedly. The physician owes the patient the courtesy of a warm pair of hands during the examination.[27]

Upon placing the patient on the examining table, the pediatric urologist can determine if the child will cooperate with the examination. In a cooperative child, the physical exam should be as thorough as possible, as there is no guarantee that the child will remain cooperative at future appointments. If the child remains cooperative, the various abnormalities identified during the examination should be demonstrated to the parents as part of their education into the child's urologic condition.

FIGURE 1.1 Vincent's curtsy.

FIGURE 1.2 Vincent's curtsy.

Age-Pertinent Factors

1. The uncooperative child and toddler
   a. When the child is uncooperative, the physician may rely on distraction techniques, such as allowing him or her to play with a penlight or toys or hold an otoscope, to console the child. It is noteworthy that many patients who are uncooperative probably have had a negative experience with a healthcare provider in the past. If the child remains uncooperative or fearful, one should try to make the best of the situation, but never force an examination on the combative child. If an acute surgical condition is suspected, and the child is uncooperative, persevering with the examination with the use of assistants to gently restrain the combative child may be necessary. A useful technique to examine the abdomen and genitalia of anxious young children is to have the mother embrace, and gently pin down, the upper torso of the child against the examination table, while an assistant places the palms of their hands on the patient's thighs, at midthigh, to keep the body in place against the examination table. The mother's body shields this child's head from the examination. This allows the examining physician to conduct a quick and effective examination while the child is reassured by the closeness to the mother.
2. The role of the chaperone
   a. The examination of the pediatric patient, whether an infant, toddler, child, or adolescent, should always be performed in the presence of a parent or guardian. In situations when the parent or guardian is not available, or when their presence may be detrimental to the patient, the presence of a chaperone as an adult member of the healthcare team should be offered to all pediatric patients undergoing potentially embarrassing or psychologically stressful examination, such as examination of the anogenital areas, reproductive organs, or breast of the adolescent female. The role of the chaperone is to "reinforce the professional nature of the interaction and content of the examination and to provide a witness in case of misunderstanding."[28] The American Academy of Pediatrics updated its policy on use of a chaperone for pediatric patients in 2011.[29]

Vital Signs

Importance of Vital Signs

A patient's vital signs are the most basic and broadly applied component of the physical exam. The four basic vital signs are heart rate, respiratory rate, temperature, and blood pressure. These signs provide a wealth of information about both the acuity of the patient's condition and its etiology. Vital signs are particularly useful because they can be followed over time, allowing a dynamic view of the course of the patient's illness. Due to their objectivity and quantitative nature, they have lower interobserver variability than many other physical exam findings, making them useful in situations in which the physician must assume care of a patient with whom he or she is not familiar—a scenario ever more common with today's resident work hour restrictions and handoffs.[30,31] Vital signs are often the deciding factor in what is perhaps the physician's most important decision—whether it is safe to send the patient home.[32]

Despite the immense value of vital signs, in a world where physicians are asked to do more in less time, the responsibility for taking vital signs often falls on other healthcare professionals, techs, or medical assistants with varying degrees of medical knowledge. Ultimately, therefore, if the physician cannot take vital signs himself or herself, he or she should ensure that the vital signs are congruent with the patient's history and other clinical findings. If any doubt arises as to the reliability of the patient's vital signs, they should be repeated.

Temperature

The median temperature in the adult population is 98.6°F, and fever is generally considered to be a temperature of >100.6°F when it is consistent with other clinical findings. Unlike other vital signs, these figures are not significantly different in the pediatric population, although the variation in normal temperature may be greater in children than in adults.

In newborn infants, the nervous system is not yet fully myelinated, limiting their ability to effectively regulate and respond to changes in core body temperature and resulting in larger temperature shifts than might be expected in other patients. Moreover, newborns do not have the ability to shiver as do older children and adults, but must rely on the metabolism in order to increase their core body temperature. Infants also struggle with thermoregulation because their ratio of surface area to mass is more than three times that of a normal adult, making them more susceptible to temperature changes in their ambient environment. For example, a newborn may present with an above-average temperature swaddled by his or her mother in a blanket, while showing a lower-than-normal temperature after lying undressed in an air-conditioned exam room for several minutes.

When considering a patient's temperature, particularly when considering short-term trends or multiple temperature readings taken close together, it is important to ensure that all temperatures were taken by the same modality (oral, rectal, tympanic, etc.).

Rectal temperature is the most reliable measure of core body temperature since it is least influenced by the ambient temperature. It is especially ideal in small children, who may have difficulty holding an oral thermometer in their mouth for the full 60 seconds that is generally required for an accurate reading. In general, oral temperatures tend to be approximately 1°F lower than rectal temperatures. This difference may be exaggerated by recent ingestion of cold substances, such as popsicles, or with an increase in respiratory rate. Thus, the physician must be aware that a tachypneic patient with a normal oral temperature may actually be febrile by rectal temperature.

Other common modalities for measuring temperature include tympanic membrane, temporal artery, and axillary. Tympanic membrane temperatures may more accurately reflect core body temperature than do oral

temperature measurements, but just like oral temperature measurements, they may at times be volatile. Obstruction of the tympanic membrane by a foreign body or, more commonly, cerumen may artificially decrease tympanic membrane temperature readings.[33]

The accuracy of temporal artery core temperatures correlates well with rectal temperature in determining fever in pediatric patients, but is less invasive and thus causes less discomfort. This modality has been extended to premature infants in the neonatal intensive care unit (NICU) setting, with the variation of placing the probe on the neck behind the ears.[34]

Lastly, axillary temperatures, although popular in the lay population, are inaccurate and should be used on a very limited basis by healthcare providers.

Heart Rate

Normal heart rate can vary widely in the pediatric population, depending on age. Normal heart rate can range from 55 bpm in the teenager to 170 bpm in a premature infant. It is therefore crucial for the pediatric urologist to consider the age of the child when analyzing heart rate.

The two main causes of tachycardia in a pediatric outpatient setting are infection and physical activity (such as a fussy or crying infant, hyperactive toddler, or anxious child). Increased sympathetic stimulation resulting from fear or medication (e.g., stimulants) may also increase heart rate. Likewise, medications such as anticholinergics may limit the ability to increase heart rate, thus masking a potential infection.

The most common location for taking a patient's pulse is the radial artery, and this is usually done by counting the beats in a 10-second period and then multiplying this figure by 6 to get the beats per minute. Alternatively, in infants and small children, where the radial pulse may be difficult to palpate, a carotid or femoral pulse may be taken instead.

Blood Pressure

Blood pressure also varies with age, although unlike the heart rate, this relationship is positively correlated with age. It is difficult to precisely define the normal blood pressure range at a given age due to differences in the rate of development. Therefore, small deviations from the expected range for a given age are usually not as significant as deviation from previous blood pressure patterns of a particular patient.

When measuring blood pressure in pediatric patients, it is crucial to use an appropriately sized cuff. A cuff that is too large will result in an artificially low blood pressure, while a cuff that is too small will result in an overestimate. Artificially low blood pressure readings can also occur due to excessive pressure with the stethoscope by the examiner, resulting in a tamponade effect on the brachial artery. This is particularly important in pediatric patients, whose blood pressures tend to be lower than those of the adult population, requiring a gentler touch.

Respiratory Rate

Similar to heart rate, the respiratory rate decreases with age, approaching an adult rate of 12–18 breaths per minute near the time of puberty. Respiratory rate may be increased by exercise or fussiness in the pediatric patient, but should return to normal within several minutes of cessation of physical activity. A persistently elevated respiratory rate with normal heart rate and blood pressure may be a sign of respiratory compensation for a metabolic acidosis, while a decreased respiratory rate may compensate for a metabolic alkalosis. Increased respiratory rate combined with increased heart rate and decreased blood pressure may be a sign of hypovolemic or septic shock. Most ominous, however, is the finding of a child with increased work of breathing and accessory muscle use, as this may signal impending respiratory failure.

Examination of the Chest, Breast, and Axilla

Examination of the Chest

As part of the physical exam, the pediatric urologist should auscultate the heart and lungs. Although this may only rarely produce novel findings, it is particularly pertinent in patients with a known cardiac anomaly or in patients with syndromic findings. It is also important in evaluating a patient's readiness for surgery, as heart conditions, thoracic cage abnormalities, or respiratory compromise may predispose the patient to anesthetic complications.

Clinical Breast Exam and Gynecomastia

In evaluating the development of a pediatric patient, the breast and axilla should be examined, as they provide key information about the effect of sex hormones on the patient's development. In the adult population, a clinical breast exam is conducted mainly on females, for the purpose of screening for breast cancer. In the pediatric population, however, a breast exam should be conducted on both males and female.

In males, the aim of the breast exam is to evaluate for gynecomastia. Gynecomastia is characterized by ductal proliferation. It is common in neonates due to an excess of maternal estrogens, in adolescents due to an imbalance in the production of estrogens or androgens, and in obese children due to excessive peripheral conversion of steroids to estrogens by adipose tissue aromatase. Pathologic conditions associated with gynecomastia include estrogen-producing adrenal gland and germ cell tumors, diabetes, and hyperthyroidism. It may also be caused by some medications.

In females, the clinical breast exam is most useful for evaluating sexual development (Tanner stage). Thelarche is the first sign of puberty in the female. It occurs, on average, between 9 and 10 years of age, and begins with elevation of the papilla (see "Growth, Development, and Tanner Stage" for complete Tanner staging). Adrenarche, the onset of androgen-dependent development of axillary hair, follows thelarche.

In pediatric female patients without a specific complaint, the clinical breast exam may be limited to inspection for the purpose of defining the developmental stage. If a gross abnormality of the breast is visible, palpation may be required, and should proceed in a manner similar

to that used in adults. Prior to beginning palpation, the procedure should be explained and permission should be asked of both the parent and the child.

In the pediatric male patient in whom gynecomastia is a concern, the breast exam should begin with inspection, although palpation is always required. This is because true gynecomastia must be distinguished from pseudogynecomastia. In true gynecomastia, breast enlargement occurs as a result of glandular and epithelial proliferation of breast tissue due to the effect of excess estrogen. In pseudogynecomastia, however, breast enlargement is purely the result of increased adipose tissue. Therefore, if true breast tissue cannot be palpated, then gynecomastia cannot be diagnosed no matter the size of the breast.[32]

Examination of the Axilla

In the pediatric patient, the axillary exam consists of inspection and palpation. Inspection of the axilla is useful for establishing the type and density of axillary hair in determining the Tanner stage. Axillary hair in a young patient may be the first sign of precocious puberty.

Unlike in adults, in whom nontender axillary lymphadenopathy may signify breast cancer, nontender axillary lymphadenopathy in childhood is both common and generally benign. It may, however, be associated with lymphoproliferative disorders and may require further investigation based on history.

Growth, Development, and Tanner Stage

Growth and Development in the Infant and Child

A newborn infant will lose a portion of his or her body weight over the first few days of life, but is expected to return to birth weight by 2 weeks of age. After this initial weight loss, a weight gain of 30 g (1 oz.)/day is expected during the first 3 months of life, 20 g/day between 3 and 6 months, and 10 g/day between 6 months and 1 year. The daily rate of growth continues (as a percent of body mass) to decline until adolescence, when individuals undergo a growth spurt.

During well-child exams, pediatricians monitor child growth using standardized growth curves indicating "normal" values for 95% of children at a given age (specialized growth charts are also available for children with certain genetic disorders, such as Down's syndrome). Failure to thrive is a condition in which a child is not gaining as much weight as expected and is defined by the crossing of two major percentile lines (e.g., 90th percentile, 75th percentile, etc.) on the National Health Statistics Growth Chart.[33] Usually, weight is affected before height. Although most failure to thrive is caused by inadequate caloric intake or absorption, it may also be caused by systemic conditions. In addition to malignancy, urological conditions that may cause failure to thrive include recurrent urinary tract infections, chronic renal failure secondary to obstructive uropathy, renal tubular acidosis, or Fanconi syndrome.

In conjunction with growth pattern, the pediatric urologist should also make a note of the motor and cognitive development of the patient. Delayed milestones in these areas may be the result of central nervous system (CNS) injury or spinal cord dysfunction and may therefore have profound effects on urinary function, specifically dysfunctional voiding. Moreover, a child with delayed language skills may be referred to the urologist out of concern for daytime wetting when in fact the child may not yet be developmentally ready for toilet training.

Growth and Development of the Adolescent

Adolescence is a period of both rapid physical growth and sexual development. During the adolescent growth spurt, children gain as much as half of their adult weight and a quarter of their adult height. The growth spurt lasts 2–3 years and occurs 1–2 years earlier in females than in males.

True puberty is defined as the time during which the hypothalamic–pituitary axis matures, leading to an increase in luteinizing hormone (LH), follicle-stimulating hormone (FSH), and gonadal sex steroids (estrogen and testosterone). It is preceded by adrenarche—the onset of adrenal steroid synthesis—by 2 years.

In males, testicular enlargement is the first sign of puberty and occurs between 11 and 12 years of age. The growth of pubic hair occurs next and is followed by growth of facial or axillary hair 2 years later.

In females, puberty begins with thelarche (the development of breast buds) between 9 and 10 years of age. It is followed by pubic hair growth, and finally menarche between 12 and 13 years of age.

Tanner staging serves as a metric for monitoring the development of pubertal growth and sexual maturation. This staging system or scale is named after the British pediatric endocrinologist Dr. James M. Tanner, who examined a group of females every 3 months over two decades as a longitudinal study of pubertal growth. He went on to categorize these patients into five stages that represent a continuum of pubertal growth.[35] Tanner stages for both males and females are routinely used to assess normal and abnormal pubertal growth.[36] The Tanner stages as a classification of sexual progression define the changes of the external genital development in boys, breast development in girls, and pubic hair appearance in both boys and girls. The charting of these changes has been replicated in many references, and essentially can be summarized as follows:

Genital development (boys)

- *Stage I*: Prepubertal
- *Stage II*: Testes and scrotum enlarge and scrotal skin becomes thicker
- *Stage III*: Enlargement (elongation) of penis and further testicular growth
- *Stage IV*: Darker skin, increase in girth of glans and penis, continued growth of scrotum and testes
- *Stage V*: Adult genitalia

Breast development (girls)

- *Stage I*: Prepubertal
- *Stage II*: Elevation of breast and papilla (nipple) to produce a breast bud
- *Stage III*: Continued enlargement of the breast and areola with a smooth contour

- *Stage IV*: Papilla and areola form a secondary mound above the level of the breast
- *Stage V*: Adult stage with projection of papilla and recession of areola

Pubic hair (boys and girls)

- *Stage I*: Prepubertal (if hair is present, it is similar to abdominal wall hair)
- *Stage II*: Sparse appearance of pigmented hair, straight or curled; first noted at base of penis or along labia majora
- *Stage III*: Hair pattern is darker and curled, coarser, migrating to skin overlying symphysis pubis
- *Stage IV*: Hair is similar to adult distribution but in a slightly smaller area than for the adult
- *Stage V*: Adult hair distribution, more abundant

Abdominal Exam

General Abdominal Exam

Thorough examination of the abdomen requires inspection, palpation, and auscultation. In the abdomen, auscultation should always precede palpation, as palpation may decrease the tone of the bowel loops, resulting in decreased bowel sounds. Secondly, palpation of the abdomen is more irritating than auscultation, and in cases where the abdomen is acutely tender, the patient is more likely to decline further examination following palpation, rendering the abdominal exam incomplete. Detection of an abdominal mass may be the first manifestation of a pathologic or nonpathologic process, such as a distended bladder, a multicystic dysplastic kidney, a hydronephrotic kidney, or Wilms' tumor.[37]

When inspecting the abdomen, the physician should note both the contour of the abdominal wall and any skin markings. A scaphoid abdominal contour may indicate malnutrition or cachexia (malignancy), while a localized protuberance of the abdominal wall generally indicates distention of one or more intra-abdominal organs. For example, a protuberance in the hypogastrium may indicate distention of pelvic organs, such as the bladder (outlet obstruction or dysfunctional voiding). In infants or small children, a localized abdominal protuberance may also be the result of a solid tumor, such as neuroblastoma or Wilms' tumor.

In children with a history of constipation, urinary tract infection, or dysfunctional voiding, the abdomen should be palpated for hardened stool. Stool is most easily palpable in the left lower quadrant (sigmoid colon), although it may be palpable throughout the abdomen.

Normal-sized healthy kidneys are difficult to palpate in older children and teenagers because they are overlapped by the diaphragm and ribs and covered by thick musculature of the abdomen and back. In younger children, the kidneys may be palpable on deep inspiration, particularly on the right, where the kidney sits approximately one vertebral level lower (L1-L4 vs. T12-L3 on the left) due to the presence of the liver during development. Palpation of the kidney is best achieved with a bimanual technique, asking the patient to inhale and exhale deeply while progressively applying deeper palpation in the subcostal areas.

FIGURE 1.3 Abdominal mass.

In neonates and small infants, it is possible to use a single-handed technique by grasping the patient's flank between the thumb (anteriorly) and fingers (posteriorly over the costovertebral angle). At the point of deepest inspiration, bring the thumb in opposition with the fingers, trapping the kidney in between.

In children, over half of the palpable abdominal masses are of renal origin (Figure 1.3). A solid and therefore potentially malignant mass (Wilms' tumor or neuroblastoma) may be occasionally distinguished from a cystic mass (hydronephrosis, polycystic kidney disease, or multicystic kidney disease) by transillumination. This can be accomplished by placing a flashlight against the costovertebral angle on the side of the mass and examining the anterior of the abdomen. Since cystic masses are filled with fluid, they scatter light rays and appear to glow. Solid masses are opaque and will prevent transmission of light. Transillumination is most reliable in younger infants and newborns, as skin thickness, and as a result opacity, increases with age.

With regard to the physical examination of pediatric malignant masses, neuroblastoma typically presents as a firm, irregular mass, which crosses the midline due to its propensity for dissemination and multiple potential sites of origin. Conversely, Wilms' tumor typically presents as a mobile abdominal and flank mass, which does not cross the midline.

In patients with symptoms of urinary tract infection, pyelonephritis should be ruled out. Pyelonephritis, or any condition that distends the renal capsule (stone, perinephrenic abscess, etc.), will cause tenderness at the costovertebral angle.

Examination of the Bladder

The bladder is amenable to examination by both palpation and percussion. Palpation of the bladder should begin at the umbilicus and move caudally toward the symphysis pubis. The bladder is rarely palpable in most patients. A palpable bladder may be soft or tense, depending on its volume and also on the thickness of the detrusor muscle. The finding of bladder distension should prompt further evaluation for bladder outlet obstruction, neuropathic bladder, incomplete bladder emptying, or urinary retention (Figure 1.4).

FIGURE 1.4 Palpation of distended bladder.

Significant bladder distension may be visible even on inspection as convex protuberance in the hypogastric region. If bladder distension is suspected based on physical exam, additional evaluation with ultrasound is warranted.

Genital Examination

Importance of the Genital Exam

The genital exam is not only the specific domain of the pediatric urologist, whose expertise in examining this area surpasses that of any other specialist, but also a part of the physical exam that is conducted less frequently by the generalist due to its intimate nature. Therefore, missed diagnoses in this area can go unnoticed for longer periods of time than other more readily accessible physical areas. In addition, many genital issues are congenital in origin and best repaired when the child is young. Finally, some genital conditions (undescended testes and disorders of sexual differentiation), whether repaired early or not, may have a significant medical and psychosocial effect on the patient later in life if they go undiagnosed.

Examination of the Scrotum and Its Contents

Examination of the scrotum begins, like other areas of the body, with inspection. Inspection may not only identify rare congenital malformations, such as disorders of sexual differentiation, but also provide insight into more common conditions. The inguinal and scrotal areas can be assessed simultaneously, looking for asymmetry, hernias, hydroceles, and undescended testes. Hydroceles should be closely examined to ensure that the testes can be palpated. Transillumination is frequently performed to demonstrate a fluid-filled hydrocele sac (Figure 1.5). Failure to identify a testis by palpation in a patient with a tense hydrocele should always prompt further evaluation with a scrotal ultrasound regardless of the results of transillumination, but particularly when transillumination suggests a solid mass[38] (Figure 1.6). The position of the testes in the scrotum should be observed prior to touching the patient, and invariably descended and retractile testes will be visible prior to palpation. Placing a hand over the inguinal area at the pubic tubercle before touching the scrotum will prevent

FIGURE 1.5 Transillumination of a scrotal hydrocele.

a retractile testis from ascending into the inguinal area in response to the cremasteric reflex, and allow the examiner to distinguish a retractile from an undescended testis (UDT) (Figure 1.7a and b). The examination of the scrotal contents

FIGURE 1.6 Testicular mass.

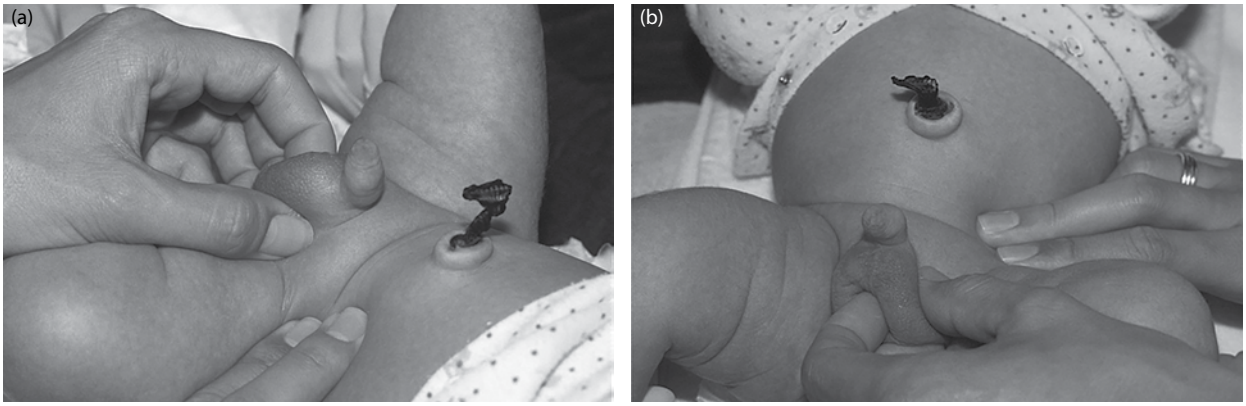

FIGURE 1.7 Two-handed examination for undescended testis (UDT).

should be performed during each visit despite the findings of scrotal testes on an earlier visit, to exclude the possibility of testicular ascent.[39] When examining a child for an undescended testis, gliding the soap-lubricated examining fingers over the child's inguinal area will often reveal the location of the testis, allowing the examiner to distinguish a palpable undescended testis from a nonpalpable testis. As the boy reaches adolescence, the first sign of puberty is the growth of the testes, which usually occurs around 11–12 years of age, corresponding to Tanner stage II.

During the examination of the scrotal contents, it is important to determine if the testes are symmetrical in size and appropriate for age and Tanner stage, as well as the consistency of the testes. Variations in size and consistency may point toward the presence of abnormalities, such as a testicular tumor, a clinically significant varicocele, atrophic testis in a patient with a previous orchiopexy or hernia repair, dysgenetic testes, vanishing testis syndrome, XX male syndrome, fragile X syndrome, precocious puberty, delayed puberty, and congenital adrenal hyperplasia.

As part of the examination, it is valuable to gauge the size of the testes. There are two distinct commercially available orchidometers that can be used to estimate testicular volume, and the examiner should ideally have these measuring tools available during the genital examination of the male patient (Figures 1.8 and 1.9). In the absence of these tools, a plastic ruler or a tissue caliper can offer some sense of testicular size (Figure 1.10). The most popular orchidometer is the Prader orchidometer, first popularized by Dr. Andrea Prader in 1966.[40] This orchidometer consists of a string holding a group of 12 oval beads graduated from 1 to 25 cc that are used to match the size of the patient's testis to estimate testicular volume (Figure 1.8). Another type of orchidometer, the Rochester orchidometer, consists of a number of elliptical "rings" through which the testis is placed to estimate volume[41] (Figure 1.9). Both of these devices can provide a general estimation of volume and symmetry during the exam. Any abnormalities detected during the examination should prompt a more precise and accurate assessment of testicular volumes with scrotal sonography, which has been shown to be superior in the assessment of testicular volume than either the Prader or Rochester orchidometer.[42–44] Paltiel and collaborators compared various formulas to estimate testicular volume based on sonographic measurements in a canine model, and they determined the Lambert formula, first described in 1951 (Length × Width × Height × 0.71), to be the most accurate and reliable.[43,45] The formula for a prolate ellipsoid ($\pi/6 \times$ Length × Width × Height) also has been used to calculate testicular volume based on sonographic measurements.[46] These formulas and estimation of volume can be useful to the clinician to follow testicular growth and

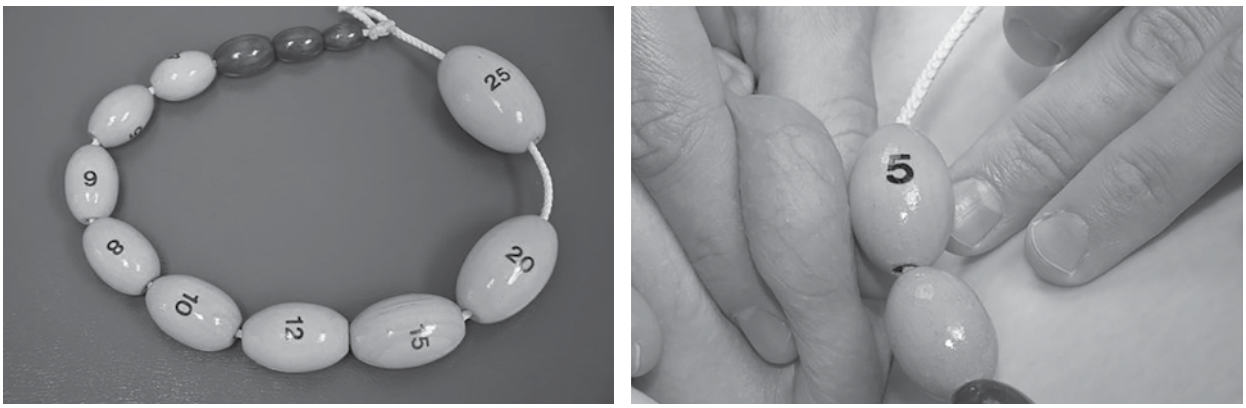

FIGURE 1.8 Prader orchidometer being used (right panel) to measure the testis volume by comparison with elliptical beads of varying sizes.

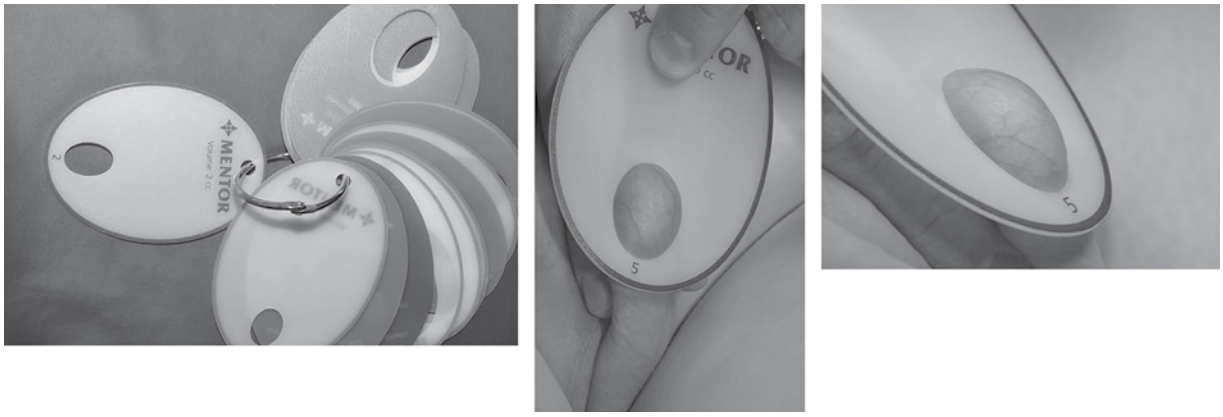

FIGURE 1.9 Rochester orchidometer being used in right upper and lower panels to measure the volume of the testis by placement of the testis through the opening.

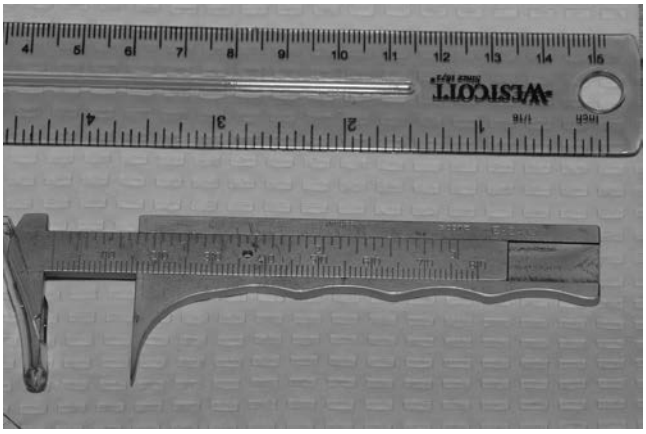

FIGURE 1.10 Ruler and caliper.

FIGURE 1.11 A varicocele is seen in the left hemiscrotum of an adolescent boy.

symmetry consistently during puberty. Assessing the testicular volume with either orchidometer can yield larger volumes than are obtained sonographically due to the inclusion of scrotal skin and epididymis, artifacts that can be overcome with experience with the orchidometers. In a study of 769 boys aged 6 months to 18 years, Goede and collaborators demonstrated an accurate correlation between volume measurements by ultrasound and by the Prader orchidometer, and concluded that "the Prader orchidometer can be used as a valid parameter for monitoring testicular growth."[46] Chipkevitch described a model to assess pubertal growth similar to the Tanner scale, in which he described various average testicular volumes for a given stage.[47] The "genital stages" correspond to similar stages in the Tanner scale. Based on a graphic model developed by Chipkevitch to assess testicular volumes, the expected testicular volume for the different pubertal stages is[48]

- *Stage I (G1)*: Volume less than 1–3 cc
- *Stage II (G2)*: Volume between 4 and 8 cc
- *Stage III (G3)*: Volume between 9 and 12 cc
- *Stage IV (G4)*: Volume between 13 and 16 cc
- *Stage V (G5)*: Volume greater than 16 cc

In a cross-sectional, population-based study, Tomova and coauthors evaluated a large population of patients for testicular volume (using a Prader orchidometer), penile size (length and circumference), body weight, and height.[49] This recent reference may serve as a contemporary range for the assessment of testicular volumes during puberty.

On physical exam, varicocele can be differentiated from noncommunicating hydrocele largely based on appearance. Varicocele is a dilation of the pampiniform plexus and internal spermatic vein due to incompetent internal spermatic vein valves. It is painless, is more common on the left side, and has a characteristic "bag of worms" appearance (Figure 1.11). Varicoceles may not be apparent unless the patient is standing up, and the examination of a pubertal and postpubertal male should always include evaluation of the scrotum while the patient is standing.[50] Noncommunicating hydrocele also presents as a nontender unilateral scrotal swelling but has a visibly smoother contour, and is not as susceptible to fluctuation due to positional changes, as it is a closed space and therefore more difficult for the fluid to escape.

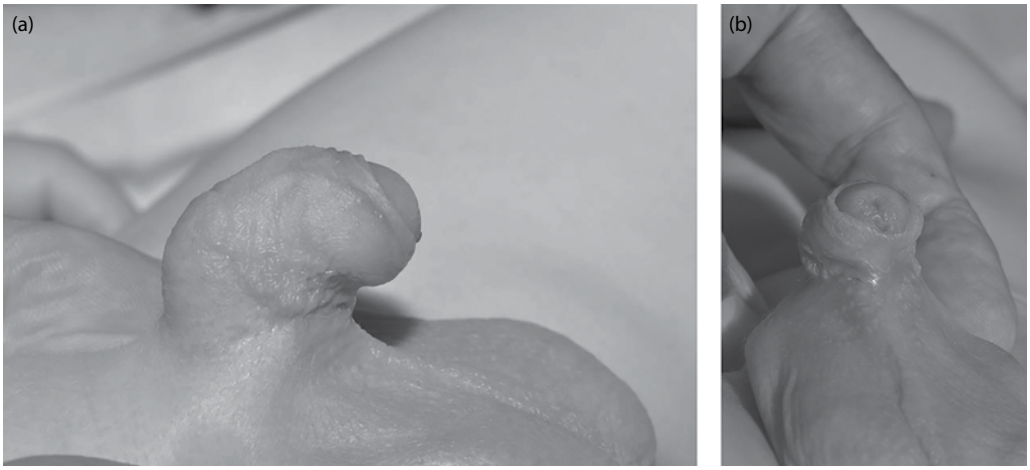

FIGURE 1.12 Chordee.

FIGURE 1.13 Ectopic hypospadic meatus.

FIGURE 1.14 Glanular (penile) adhesions.

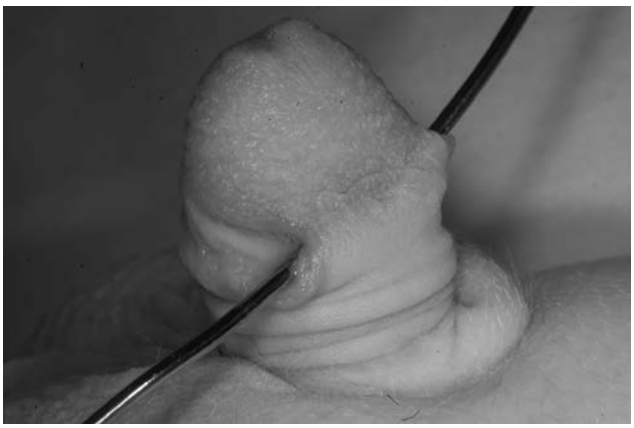

FIGURE 1.15 Dorsal skin bridge to the glans following newborn circumcision.

Examination of the Penis

In the male patient, the examination of the penis is conducted next. The child to this point should be comfortable with the exam, and the transition to the examination of the penis should be painless and well tolerated by the patient. The presence of a foreskin and appearance of the glans should be noted, as well as the presence of any penile abnormalities, including hypospadias, penile torsion, and chordee (Figure 1.12). Occasionally, the urethral meatus may be in an ectopic location in boys with hypospadias (Figure 1.13). In circumcised boys, the glans should be assessed for the presence of mucosal adhesions (Figure 1.14) or skin bridging (Figure 1.15). A hidden or congenitally buried penis (Figure 1.16a) should be differentiated from the rare but far more serious micropenis, which it might sometimes mimic (Figure 1.16b). When a micropenis is suspected, measurement of the stretched penile length with a ruler is necessary, while pressing the prepubic fat away. If the child remains cooperative, the various abnormalities identified during the exam should be demonstrated to the parents as part of their education

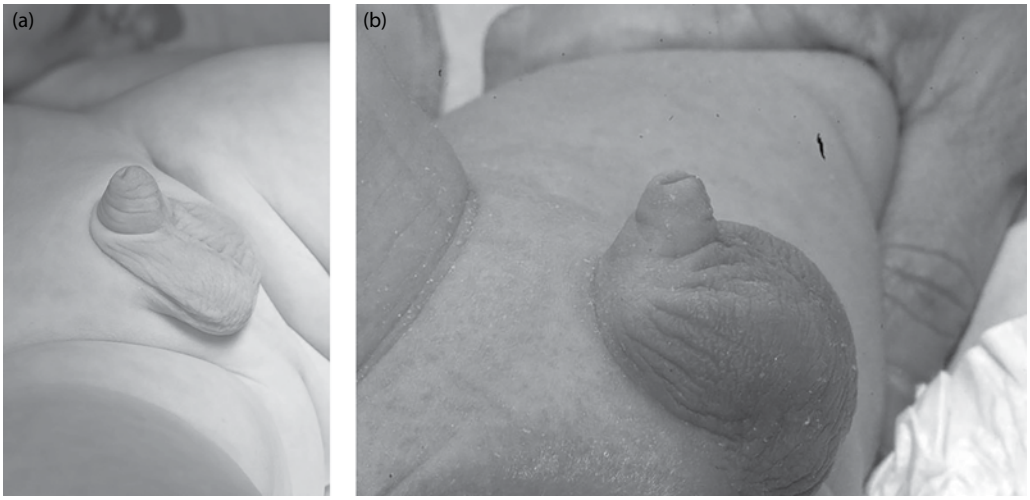

FIGURE 1.16 Hidden (concealed) penis (a), which mimics a micropenis (b).

into their child's urological condition. In the normally uncircumcised male, the foreskin should be retractile by 5 years of age, although some residual glanular preputial adhesions may remain at that age. Gentle, atraumatic retraction of the prepuce should be attempted. The prepuce should be assessed for the phimosis, and the presence of a pale, thick, annular scar suggests lichen sclerosus (Figure 1.17). Observation during urination, an important component of the physical examination, should be done to assess for possible ballooning during urination (Figure 1.18) in phimosis, or deflection of the urinary stream in meatal stenosis (Figures 1.19 and 1.20), while the boy pushes the penis down to direct the stream into the toilet bowl. The opportunity to assess a boy during urination invariably yields relevant information about the patient's condition, such as the caliber and orientation of the stream, presence of abdominal straining, interruption of the flow (staccato pattern) or intermittency, and postvoid dribbling. Some boys with "wetting" may be discovered to rush through voiding by barely lowering the waist of the pants to the penoscrotal junction, and then bending the penis over this obstacle, in essence entrapping the penis in an awkward position. Upon completion of urination and returning the penis to the normal anatomical position inside the underpants, the distended urethral bulb empties into the underpants, thus the wetting. The location and size of the meatus should be noted, remembering that a small meatus on examination is not always indicative of urethral meatal stenosis (Figure 1.20). The appearance of the deflected urinary stream during the assessment of the urinary flow in the toilet-trained patient will confirm if urethral meatal stenosis is present[51] (Figure 1.20).

FIGURE 1.17 Phimosis and annular cicatrix suggesting lichen sclerosus.

Examination of Penile Size and Micropenis

A micropenis is defined as a penis that is 2.5 standard deviations below the mean for a given age, without any hypospadic abnormalities. A micropenis is typically normally proportioned, with an appropriate ratio of shaft diameter to length (Figures 1.21 and 1.22). By this definition, the penis should measure at least 1.9 cm in a newborn, full-term infant to be considered normal.

The pediatric urologist is often consulted to evaluate a small penis in three rather distinct clinical scenarios. The first scenario is that of the newborn who does not undergo a neonatal circumcision because of the small-appearing penis. In this situation, it is critically important to differentiate a micropenis from a congenitally buried penis (Figure 1.23). A second scenario is that of the child who appears to have a small penis, which could represent a micropenis or a hidden penis secondary to prominent prepubic fat (Figures 1.24 and 1.25). The last scenario is that of the older prepubertal child whose somatic growth exceeds genital growth and the discordant growth creates concern about the size of the apparent "buried" and small penis (Figure 1.26). An inadequate or small-appearing penis may cause significant anxiety in both parents and the affected child. The topic must therefore be discussed with great care, whether or not the concern about penis size is well founded. The pediatric urologist should appropriately measure the length of the penis, even in cases where the diagnosis of micropenis appears unlikely, as a quantifiable discrepancy between the child's penile length and a length that would constitute micropenis may alleviate some of the concerns of the parents. In a child with below-average penile length, the

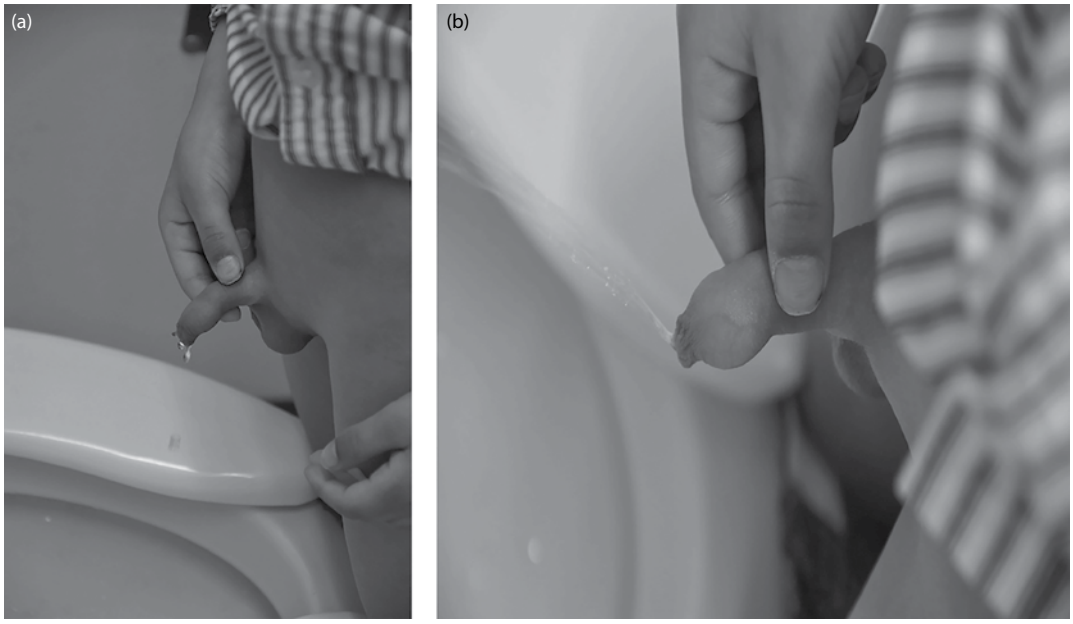

FIGURE 1.18 Ballooning of prepuce during urination.

physician should emphasize that the penis is of "normal size" rather than focus the conversation on what the mean length ought to be.

The standard method of measuring penile length is to lay the child in the supine position and place one end of a plastic ruler, flexible tape measure, or caliper on the pubic symphysis at the base of the penis (Figure 1.27). The examiner may then use his or her other hand to stretch the penis, measuring the distance between the pubis and the tip of the glans.[52] The reason the penis must be stretched is because stretched length, rather than relaxed penile length, more closely correlates with the length of the erect penis (Figure 1.27) (Video 1.1).

FIGURE 1.19 A boy with urethral meatal stenosis demonstrates the typical fine-caliber stream and the need to point the penis downward, toward the floor, in order to target the toilet.

An alternative, although less commonly used, method of measuring penile length in infants is with the aid of a modified syringe. In this technique, the needle end of a disposable 10 mL plastic syringe is cut and the piston is inserted into the cut end. The flanged end is then placed over the penis and pressed firmly into the pubis, creating a seal. The piston is then pulled back, drawing the penis into the barrel, partly erect. This excludes the supra pubic fat and allows the penile length to be noted on the scale printed on the syringe. Proponents of this method believe it to be less prone to individual variation than the standard method outlined above[53] (Figure 1.28).

Finally, penile length may be measured sonographically by using ultrasound to measure the length of the corpora.[54]

In obese children, the penis may appear smaller than its measured length due to a large suprapubic fat pad, which allows only a small portion of the penis to protrude beyond the abdominal wall. Likewise, patients with buried penis or webbed scrotum may be mistakenly diagnosed with micropenis. In buried penis, there is a deficiency of penile shaft skin and an abnormal attachment of the dartos fascia to Buck's fascia, causing entrapment of the penis in the subcutaneous tissue. In webbed scrotum, the scrotal sac attaches to the shaft of the penis at the ventral aspect of the shaft rather than the base of the penis, making the penis appear smaller[55] (Figure 1.29).

Common causes of micropenis include testosterone deficiency (or insensitivity) syndromes, abnormalities of the pituitary–hypothalamic axis, or cloacal exstrophy. Micropenis is also associated with chromosomal abnormalities, such as Down's syndrome, Klinefelter's syndrome, and Prader–Willi syndrome. Lastly, many cases

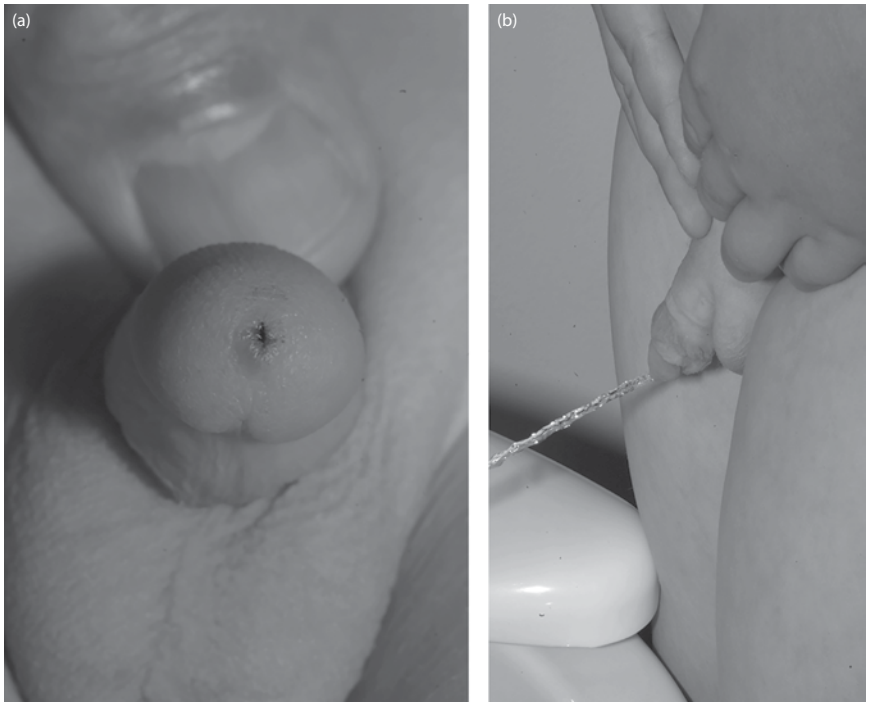

FIGURE 1.20 A boy with urethral meatal stenosis demonstrates the typical fine-caliber stream and the need to point the penis downward, toward the floor, in order to target the toilet.

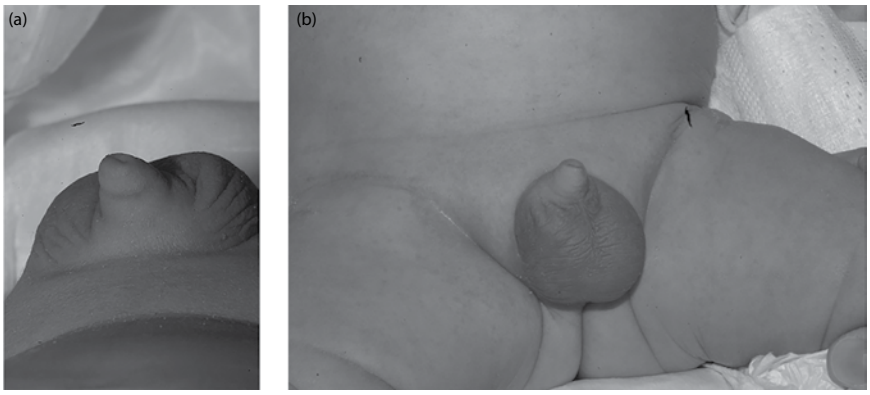

FIGURE 1.21 Micropenis.

FIGURE 1.22 An infant with congenital hidden penis demonstrates a penile length of *at least* 1.9 cm.

FIGURE 1.23 Infant with congenital hidden penis.

FIGURE 1.24 Boy referred for micropenis whose phallus is hidden by redundant penile skin and a prominent suprapubic fat pad. Hidden penis.

do not present with associated abnormalities, and are referred to as idiopathic micropenis. All these cases warrant a careful endocrinological evaluation.

Examination of the Vulva

The vulva consists of the external genital organs of the female. These include the mons pubis, labia majora, labia minora, clitoris, vulvar vestibule, urethral meatus, hymen, and genital glands (sebaceous, Skene's, and Bartholin's). During the physical examination, the vulva should be carefully inspected and any visible abnormalities palpated. Prior to beginning the examination, permission should be asked of the parents and the steps of the exam should be described. It is prudent to have a female nurse or other healthcare provider present as a chaperone during the exam. Examination of the genitalia in the preadolescent female is best conducted in the supine position with the legs in a frog-like position, with the soles of the feet touching each other. If this is not satisfactory, then a knee–chest position, asking the patient to perform Valsalva's maneuver, will allow satisfactory inspection of the introitus.[56] This should be the last part of the examination, and the girl may remain clothed until then. Practicing this part of the exam with a nurse prior to the physician conducting the genital exam may reduce the girl's apprehension related to the exam. To this effect, we often will tell the patient that a nurse is coming to help her undress and to teach her a task. Talking to the girl and explaining what we are doing in a friendly, but professional, manner is also helpful in comforting the patient. Depending on the age of the patient, the examination can be conducted while the girl remains in her mother's lap. If the child is placed on the exam table, the mother is encouraged to bend over to embrace the child and offer additional comfort. Distracting the child with a stethoscope or other toy and soliciting the help of the parents to comfort the child may go a long way in aiding relaxation. We ask the girl to try to touch the wall against the table with her knee, effectively encouraging her to flex and abduct her hips. After observing the external genital appearance, the labia majora are firmly, but not tightly, grasped between thumb and index finger, and pulled outwards and upwards, allowing full assessment of the open introitus, distal vaginal canal, and urethral meatus[57] (Figures 1.30 through 1.35). Any discharge or pooling of urine in the introitus should be further assessed with appropriate imaging studies. A pelvic examination, if necessary in the prepubertal female, should be conducted under general anesthesia, as manipulation and insertion of fingers or devices may have long-lasting psychologic consequences. Upon completion of the examination of the introitus, the girl is placed on her side to assess the appearance of the anus, as well as the cutaneous and bony aspects of the low back. Attention should be given to the presence of dimples, scoliosis, discolored skin patches, or hairy nevi in this area. The examination of the lower extremities completes the examination, and particular attention should be given to symmetry, strength, and skin temperature. The degree of estrogenization may be inferred by examining the female escutcheon. This is of particular importance when precocious or delayed puberty is suspected, and can be quantified by Tanner staging (see above).

The vulvar skin should be examined to look for changes such as erythema, edema, excoriations, ulceration, bullae, or rash. Such lesions may be due to a variety of causes, from trauma to sexually transmitted infection to contact dermatitis to chronic irritation due to urinary incontinence. A painful ulceration in an adolescent is most likely due to coalesced herpes simplex lesions or, less commonly, chancroid, while a painless ulcer is likely due to syphilis. Multiple flesh-colored papules and/or small

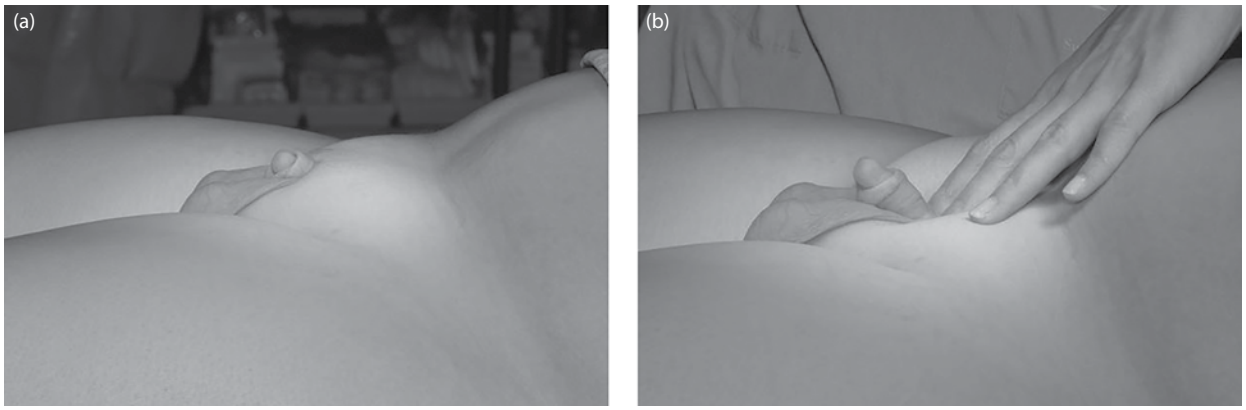

FIGURE 1.25 Boy referred for micropenis whose phallus is hidden by a prominent suprapubic fat pad. The normally sized phallus is demonstrated by pressing on the fat pad.

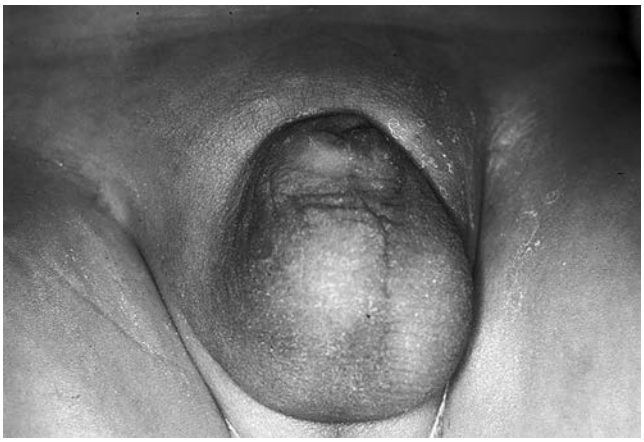

FIGURE 1.26 Boy with concealment of his penis because of prominent suprapubic fat and scarification of penile skin.

FIGURE 1.27 Measurement of micropenis.

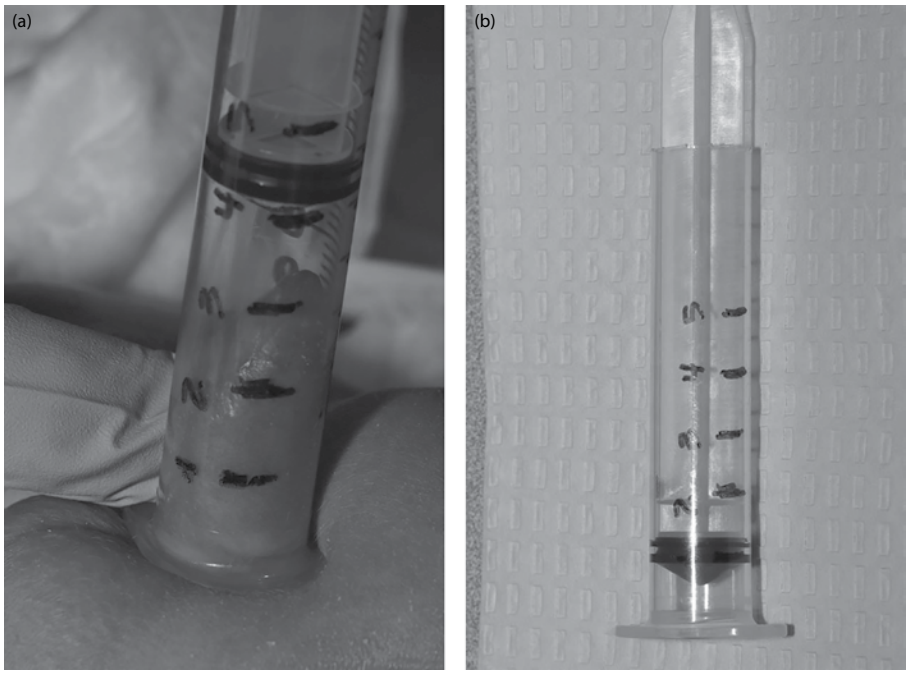

FIGURE 1.28 Ozbey penile measuring tool.

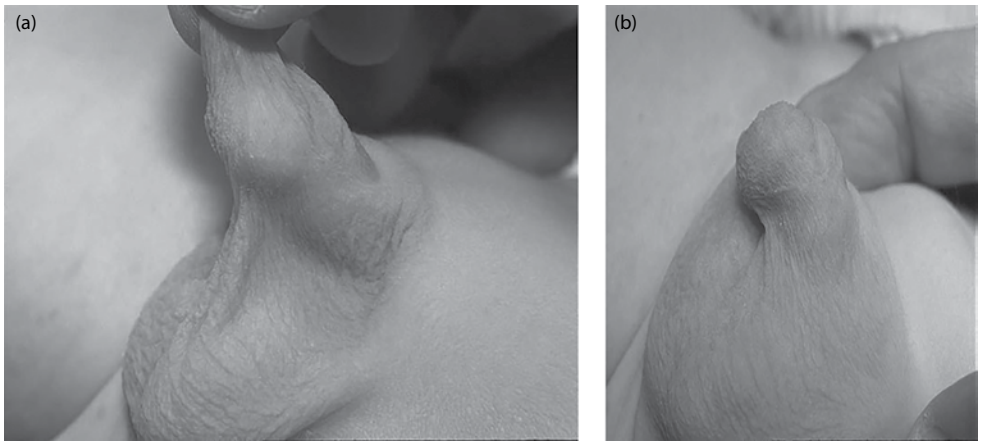

FIGURE 1.29 Penoscrotal web.

FIGURE 1.30 Neonatal introital exam.

FIGURE 1.31 Infant vulva.

FIGURE 1.32 Infant vulva.

FIGURE 1.33 Introital exam of a child.

cauliflower-like lesions (condyloma accuminata) are the result of human papillomavirus (HPV) infection.

When there is a history of labial or inguinal swelling, the labia should be palpated to rule out hernia (Figure 1.36). The inguinal lymph nodes should also be examined, as palpable inguinal nodes signify infection or cancer.

In patients in whom sexual abuse is suspected, the hymen should be examined for tears or other signs of trauma. In patients with delayed menses and normal secondary sexual characteristics, imperforate hymen should be ruled out.

In sexually active patients, the edges of the introitus should be examined for evidence of vaginal discharge, which may be the result of bacterial vaginosis or sexually transmitted infection. Classically, the discharge from

FIGURE 1.34 Introital exam of an older girl.

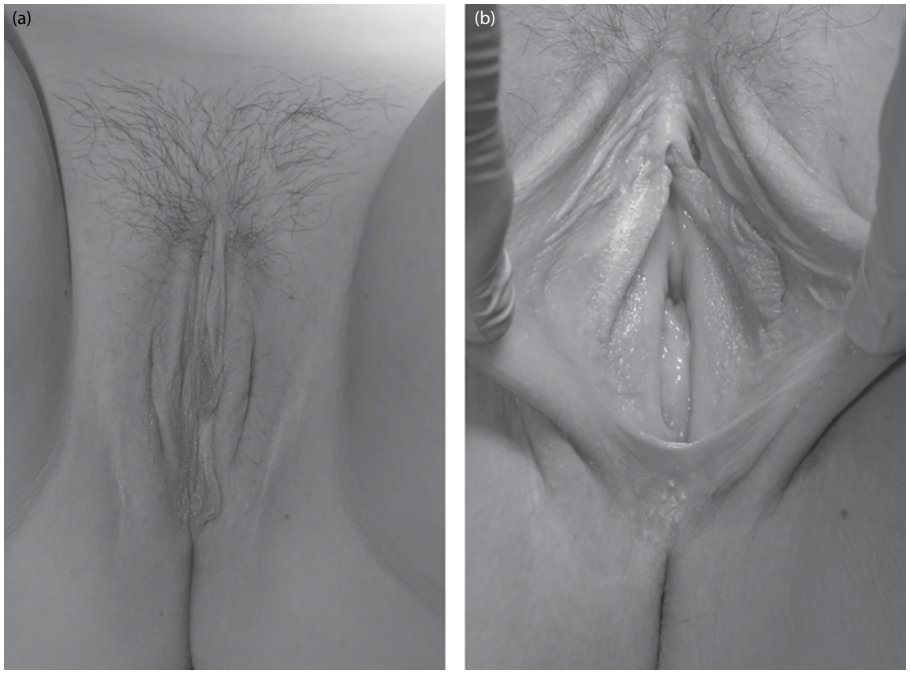

FIGURE 1.35 Female Tanner stage III.

chlamydia is described as mucopurulent, while the discharge from gonorrhea is purulent, although in reality they may be difficult to differentiate. The absence of discharge, however, does not rule out infection.

In patients complaining of dysuria, the urethral meatus should be examined for lesions, prolapse (Figure 1.37), and discharge. Discharge may be a sign of urethritis and should be sent for gram stain and culture.

The clitoris should be examined for signs of virilization. This is of particular importance in newborns, in whom a virilized clitoris may be a sign of inappropriate sexual development (disorder of sexual differentiation) (Figure 1.38). However, normal-appearing genitalia at birth do not guarantee normal sexual development. Patients with nonclassical (late-onset) 21-B-hydroxylase deficiency may present during later childhood or puberty with abnormal pubertal development and virilization.

In preadolescent girls, a speculum is usually not required. If there is an acute trauma or active vaginal bleeding, such an exam should be performed under anesthesia.

FIGURE 1.36 Bilateral inguinal hernias in a female.

FIGURE 1.37 Urethral prolapse.

FIGURE 1.38 Clitoromegaly.

This will allow for a thorough exam while minimizing trauma, both physical and psychological, to the patient.

Examination of the Anal Region

The anal region may be examined in a variety of positions, with supine being the most common in small children. As long as the entire anal area can be clearly visualized, the position that is most comfortable for the patient should be utilized.

Examination of the anal region is largely based on inspection. A rectal exam is rarely required. A digital rectal examination should be reserved for special circumstances, such as a patient with urinary retention, assessment of the neurologically impaired child, or in cases of severe constipation, and it is best performed using a well-lubricated, gloved, small fifth finger. If the digital rectal exam is necessary but not possible in the office setting, the examination should be conducted under anesthesia. In patients with spinal cord injury, the bulbospongiosus reflex should be assessed by squeezing the glans or clitoris and sensing for an anal sphincteric contraction.

The anal region (as well as the perineum) should be carefully inspected in any child with fecal or urinary incontinence.

In patients complaining of pain in the anal region, a broad differential diagnosis may be easily narrowed by physical exam. For example, children who have pain in the anal region due to chronic constipation may have anal tears or fissures on exam from the passage of hard stools. Examination of a child who refuses to sit on his or her buttocks may reveal a pilonidal cyst or hemorrhoids. Acute onset of anal pain in a young child while unsupervised may reveal a foreign body or trauma. In cases of anal trauma, sexual abuse should be considered, particularly if the history is unclear.

Examination of the Back

For the pediatric urologist, examination of the back consists of two distinct components: evaluation of the kidneys and evaluation of the spine. Evaluation of the kidneys should begin with evaluation of the patient's posture. Abnormalities of the spine are significant because they are associated with tethered cord, spina bifida, and other spinal cord lesions, which can profoundly affect bladder function. Examination of the spine should always begin with evaluation of spinal curvature. This is best done by examining the patient's bare back with the patient first in the seated and then in the standing position. Abnormal curvature of the spine is possible in the frontal plane (scoliosis), as well as the sagittal plane (kyphosis or lordosis). The more significant the curvature, the more likely it is that the patient will possess neurologic deficits.

Examination of the patient's back for signs of abnormal spinal development should be carried out in all newborn infants and children with bladder dysfunction. These signs can range from subtle to profound. Subtle signs of spinal defects include a sacral dimple, patch of hair, hemangioma (Figure 1.39), lipoma, aberrant gluteal cleft, or decreased tone of the anal sphincter. If any of these signs are present, further imaging should be pursued. Conversely, some open spinal cord defects, such as myelomeningocele, may be grossly visible and should be referred for neurosurgical intervention as soon as possible.

Examination of the Extremities

Examination of the extremities is less pressing than other aspects of the physical exam. Still, the extremities provide useful information that can aid in the diagnosis of various urological conditions.

Most obviously, the extremities are useful for the examination of vital signs. A discrepancy in the strength of the pulse bilaterally or between the upper and lower body may point to coarctation of the aorta. Hemangiomas on the skin of the extremities may disclose arteriovenous malformations

FIGURE 1.39 Sacral hemangioma.

that can affect the renal arteries. Unexplained paralysis or parasthesias of the extremities may aid in localizing a spinal cord lesion that may concomitantly affect bladder function. The finding of club feet should prompt further neurosurgical and orthopedic evaluation. The finding of extremity asymmetry or hemihypertrophy should prompt sonographic evaluation of the kidneys for association with Wilms' tumors. Finally, congenital limb defects, particularly of the radius, may be a manifestation of VACTERL association.

Neurological Exam for the Pediatric Urologist

An uncomplicated neurologic examination can be easily performed in most children, and in the context of the urologic patient, this part of the examination is usually reserved for patients with voiding disorders. Normal-appearing patients with genital disorders will rarely have neurologic conditions that can be uncovered by the urologist, and neurologic examination of the infant and young child by the urologist is usually unnecessary. In the older child and adolescent, the neurologic exam should include assessment of mental status, muscle tone and strength, reflexes, cerebellar function, and sensory responses.

Muscle tone is the degree of resistance of a patient's muscles to passive motion. A patient's muscle tone may be normal, hypertonic, or hypotonic. Hypertonia is generally the result of an upper motor neuron lesion, while hypotonia generally results from lower neuron lesions. The two most common types of hypertonia include spasticity, where the resistance of a muscle increases progressively as the muscle is stretched, often followed by a "clasped knife" phenomenon in which there is a sudden release of tone following the point of maximal tone, and rigidity, where there is resistance through the full range of motion of a muscle. Particularly pertinent to the urological exam is the tone of the anal sphincter, which may be appreciated by digital rectal exam. Abnormal tone of the anal sphincter suggests similar changes in the urinary sphincter and may be the result of neurogenic disease.

Muscle strength is the ability of the patient to generate the contraction against resistance. It is characteristically measured on a scale of 0–5. A score of 0/5 indicates no contraction, such as in a completely paralyzed muscle group. A score of 1/5 indicates muscle twitching or slight contraction but no visible movement of the joint itself. A score of 2/5 indicates movement while not working against gravity (i.e., the axis of movement is perpendicular to the gravitational plane). A score of 3/5 indicates the capacity for movement against gravity but not against the examiner's resistance. A score of 4/5 indicates movement against some degree of examiner resistance, although the degree of resistance is less than expected. A score of 5/5 is normal strength against resistance.

Reflexes are involuntary muscle contractions elicited by muscle stretch (deep tendon reflexes) or superficial stimulation (cutaneous reflexes). Reflexes provide information about the integrity of spinal nerves at a given spinal cord level. They are graded on a scale of 0–4: 0/4 is areflexia, 1/4 is weaker than expected, 2/4 is normal, 3/4 is hyperreflexia, and 4/4 is significant hyperreflexia with clonus. In general, hyporeflexia is the result of lower motor neuron disease, while hyperreflexia results from upper motor neuron disease. The most commonly tested deep tendon reflexes include the patellar (L2-L4), Achilles (S1), biceps (C5-C6), and triceps (C7-C8) reflexes. Maneuvers that redirect the patient's attention (Jendrassik maneuver, having the patient look away while performing the exam) make reflexes easier to elicit, as they promote relaxation and prevent anticipatory suppression.

Commonly tested cutaneous reflexes include the cremasteric reflex, bulbocavernosus reflex, and anal wink reflex. The cremasteric reflex may be elicited by lightly stroking the superior-medial aspect of the patient's thigh. The expected response is an immediate contraction of the cremasteric muscle with consequent elevation of the ipsilateral testicle.

The bulbospongiosus (bulbocavernosus) reflex is an indicator of spinal cord injury involving the S2-S4 spinal nerve roots. It may also be absent in spinal shock, and is one of the first reflexes to return once spinal shock has dissipated. The bulbospongiosus reflex may be elicited by squeezing the glans penis (or tugging on a Foley catheter). The reflex response should be a contraction of the anal sphincter.

The anal wink reflex is similar to the bulbocavernosus reflex and also tests the integrity of the S2-S4 nerve roots. To elicit the anal wink reflex, the perianal skin is stroked with a sharp object (i.e., safety pin) to stimulate the cutaneous nociceptors. The result is contraction of the anal sphincter.

The cerebellum is largely responsible for the coordination of muscle movements; thus, disorders of the cerebellum result in disorders of coordination. Gross disorders of the cerebellum may be picked up by general observation and do not require special exam maneuvers. The patient may present with gross ataxia, nystagmus, or dysarthria. Patients with more subtle findings (and who are old enough to follow directions) may be more closely examined. The patient may, for example, be asked to keep a rhythm by tapping on the table, or may be asked to perform rapidly alternating movements, such as fast alternating pronation and supination of the hand. Other commonly used tests to check for cerebellar dysfunction include heel-to-shin (asking the patient to continuously rub the plantar aspect of their foot up and down the shin of their opposite leg in a smooth manner) and finger-to-finger (asking the patient to use their index finger to quickly alternate between touching their nose and then the examiner's index finger) tests.

The final component of the neurological exam is the sensory exam. In the urological patient, this is typically limited to examination of sensation in specific dermatomes (area of skin with sensation supplied by fibers from a single dorsal root). The most important dermatomes include the top of the foot (L5), bottom of the foot (S1), and perineum (S2-S4).[58,59]

DOCUMENTING THE PATIENT ENCOUNTER

The gathering of medical information occurs in many scenarios in the field of pediatric urology. The interaction with an expectant mother with a prenatally detected urologic malformation is very different from the interaction with an acutely ill boy with scrotal pain. Just as the types of questions and data gathering need to be adjusted according to a given medical scenario, so does the documentation of that

encounter. In the 1990s, the "Documentation Guidelines for Evaluation and Management Services" were developed by the Health Care Financing Administration (HCFA) and the American Medical Association, and since then, many variations of these guidelines have evolved. The guidelines, commonly referred to as the Evaluation and Management (E/M) services guidelines, were developed with the premise that medical interactions should provide specific documentation of the history, physical examination, and decision-making process, in order to be processed and reimbursed by Medicare. Each interaction, be it with a new or an established patient, is coded according to the number of items (bullets) covered during the interaction. Three broad categories are used (office visits, hospital visits, and consultations), and each of these categories is further subdivided according to a new or established interaction with a patient.[60–62] In the context of this chapter, it is necessary to mention this newer component of the medical history and physical examination, although it is not the intent of this chapter to expand on these complex and controversial coding guidelines.

MULTIMEDIA FILES AVAILABLE ONLINE (www.crcpress.com/cw/Docimo)

VIDEO 1.1 Penile measurement.

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CHAPTER
2

Laboratory Assessment of the Pediatric Urologic Patient

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INTRODUCTION

In general, laboratory assessment of the pediatric urologic patient is not as extensive as in the adult counterpart. Patients tend to be healthier, and there are no recommended routine preoperative laboratory screening tests for pediatric urologic patients. However, there are certain instances when laboratory examination in pediatric urology is invaluable. This chapter outlines the most common laboratory tests used in pediatric urology, demonstrating the clinical scenarios in which each test should be employed.

COMMONLY ORDERED LABORATORY EXAMINATIONS

Urinalysis and Urine Culture and Sensitivity

The most commonly utilized laboratory examinations in pediatric urology are urinalysis with urine microscopy and urine culture and sensitivity. These urine tests are routinely ordered to identify a potential infection prior to invasive urologic procedures. A urinalysis with urine culture is also standard of care in investigating a fever of unknown origin in the infant. The prevalence of urinary tract infection (UTI) in pediatric patients with fever of unknown origin is 5%.[1] If a UTI is identified, the child requires more extensive testing to rule out further urologic pathology or anatomic abnormalities.

When children present with symptoms suggestive of a UTI, such as dysuria, genital pain, diurnal enuresis, urgency, frequency, and urinary retention, it is important to understand that they may not have a UTI. These children may have a history of incomplete bladder emptying or a history of bladder and bowel holding termed "dysfunctional elimination."[2] A urinalysis and urine culture can help to discriminate between UTIs and the irritative voiding symptoms inherent to this group.[1] Dysfunctional eliminators may have irritative voiding symptoms secondary to their behavior, but they also have a higher risk of UTIs. When a UTI is identified, antibiotic treatment is essential acutely, but behavioral modification is the mainstay of treatment for children with dysfunctional elimination.[2,3]

It should be noted that there are certain instances in which the urinalysis should be interpreted with caution. In patients who perform clean intermittent catheterization, or who have undergone bladder reconstruction using intestinal segments, testing should be selective, as a positive urinalysis in these patients may only represent colonization with bacteria (see Figure 2.1). Antimicrobials are used when symptoms of infection, such as dysuria, pelvic pressure, and fever, accompany a positive urinalysis and urine culture. Overtreatment, however, may lead to the development of highly resistant organisms.[4–6]

Additionally, the method of collection can impact interpretation of laboratory urine tests. For example, a pediatric "clean catch" urine specimen may yield growth not necessarily representative of an infectious process. In our practice, we are careful to interpret urine collected from bagged specimens. Although a bagged specimen is a useful, noninvasive method for collecting urine from a non-toilet-trained child, this method can easily have a false-positive growth secondary to contamination from bacteria colonized on the genital and perineal skin. It is helpful when the bagged specimen results are negative, or if there is a single isolate on the culture. It is also important to obtain both urinalysis and culture, as the absence of leukocytes in a specimen with positive culture should make one suspect contamination. If it is unclear whether there is truly infection, the urine specimen may need recollection via catheterization.

Serum Blood Urea Nitrogen and Creatinine

Serum blood urea nitrogen (BUN) and creatinine are frequently obtained as measures of renal function. When interpreting these tests, the clinician must be aware of the impact of the size of the child, as well as their age. For example, the neonate's renal function is a reflection of maternal renal function at birth, and the creatinine levels remain similar to the maternal serum creatinine for the first several days of life prior to decreasing to normal infant levels. Premature neonates in particular will have higher levels of creatinine and take longer to approach infant levels than full-term neonates.

Serum BUN and creatinine yield insight into renal function both as a baseline marker and as a method of longitudinal monitoring. With the diagnosis of prenatal and

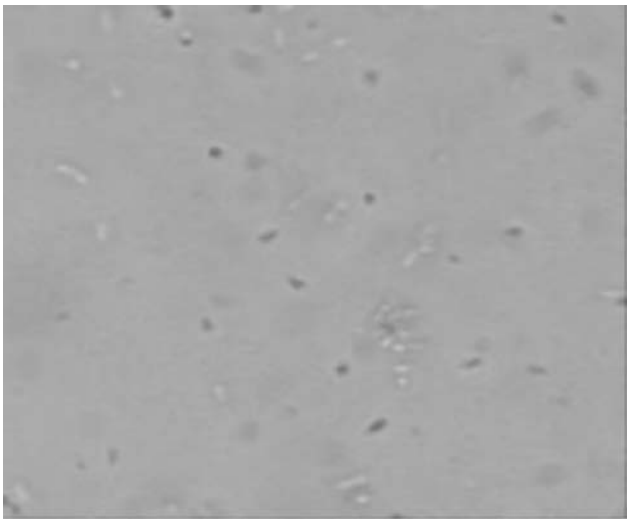

FIGURE 2.1 Asymptomatic bacteriuria. In patients on intermittent catheterization or with intestinal augmentation or diversion of the bladder, bacteria are often observed on urine microscopy. Note that there are no red blood cells (RBCs) or white blood cells visible on microscopy to indicate infection in this specimen.

perinatal abnormalities, such as oligohydramnios (potentially secondary to bilateral renal agenesis, bilateral ureteropelvic junction (UPJ) obstruction, bilateral multicystic dysplastic kidney, or posterior urethral valves) or hydronephrosis (due to UPJ obstruction, congenital megaureter, posterior urethral valves, or vesicoureteral reflux), serum BUN and creatinine are important parameters that help determine the overall prognosis, as well as in monitoring therapeutic effectiveness. For example, a serum creatinine of more than 1.0 mg/dL at 1 year of age in a child with a history of posterior urethral valves is associated with poor renal outcome.[7] Other high-risk patients that require close monitoring of serum creatinine include patients with renal scarring that can be associated with vesicoureteral reflux[8] or with a neurogenic bladder.[9]

Complete Blood Cell Count and Coagulation Studies

A complete blood cell count (CBC) and coagulation studies are not routinely obtained prior to most pediatric urology interventions. This is primarily due to the outpatient nature of pediatric urology procedures that are associated with low morbidity. There are certain patient populations, however, for whom these hematologic laboratory tests are indicated. These include children with chronic anemia, a family history of hematologic disorders, or coagulopathic tendencies.

Important preoperative hematologics tests consist of a CBC, prothrombin time (PT), international normalized ratio (INR), and partial thromboplastin time (PTT). A lower-than-average hematocrit can be seen in children with sickle cell anemia and does not necessarily require intervention. If a value represents a significant change from baseline, or if the patient is symptomatic or unstable, then hematologic intervention is recommended. Patients with platelet disorders, such as von Willebrand disease, may have an adequate number of platelets on CBC, although these platelets function poorly. In these patients, additional testing may be required, including obtaining serum levels of von Willebrand factor (vWF) VIII, vWF ristocetin cofactor activity (vWFRCo), and bleeding time (BT), in addition to CBC, PT, and PTT. Oncology patients are often pancytopenic, and procedures should be coordinated with chemotherapy cycles and administration of colony-stimulating factors, in order to maximize preoperative blood counts and minimize the chances for bleeding and infection.

Multiple clinical practice guidelines for perioperative transfusion exist for both adult and pediatric patients.[10–12] With respect to surgery, or invasive procedures, all these guidelines state the following: In the absence of associated coagulation abnormalities, a platelet count of 40,000/μL to 50,000/μL is sufficient to perform most major invasive procedures with safety. For minor procedures, a lower threshold of 10,000/μL to 20,000/μL can be used.[10–12] If platelet transfusions are administered before a procedure, it is critical that a posttransfusion platelet count be obtained to prove that the desired platelet count has been reached. Platelets should also be available on short notice in case intraoperative or postoperative bleeding occurs. In summary, hematologic values must be considered within the context of careful clinical evaluation of each individual patient, as well as the morbidity of the surgical procedure. Good communication with the pediatric hematologist will help steer the appropriate laboratory testing.

COMMON PEDIATRIC UROLOGIC CLINICAL SCENARIOS AND REQUISITE LABORATORY TESTS

Hematuria

When a child presents with hematuria, a number of tests are potentially indicated. Depending on the degree of hematuria, and whether it is gross or microscopic, there are many potential etiologies (Table 2.1). Most hematuria originates in the renal parenchyma and is termed nephrologic hematuria. It is incumbent on the urologist to distinguish nephrologic bleeding from that caused by surgically significant sources.

Hematuria is often first noticed on a urine dipstick performed at the primary care office. A microscopic analysis of the urine should follow a positive dipstick. A freshly voided urine specimen should be used for this purpose. An approximately 10–15 mL aliquot of the urine is spun in a centrifuge at 1500 rpm for about 5 minutes. The supernatant is decanted and the sediment is resuspended in the remaining liquid and placed on a glass slide with a coverslip. Careful examination of the urine sample is then conducted under high-power magnification. All noncellular and cellular elements seen should be noted and recorded. The presence of more than five red blood cells (RBCs) per high-powered field generally is considered abnormal. The detection of RBC casts is indicative of a glomerulotubular source of hematuria (Figure 2.2). The absence of RBCs and RBC casts despite a positive dipstick test is suggestive of hemoglobinuria or myoglobinuria. This is important because a positive urine dipstick for

TABLE 2.1 Differential diagnosis of hematuria in the pediatric population

Glomerular Origin

- IgA nephropathy
- Alport's syndrome
- Benign familial hematuria
- Membranoproliferative glomerulonephritis
- Acute poststreptococcal glomerulonephritis
- Rapidly progressive glomerulonephritis
- Systemic lupus erythematosus
- Membranous nephropathy
- Henoch–Schönlein purpura
- Goodpasture's disease
- Focal segmental glomerulosclerosis

Interstitial and Tubular Origin

- Acute interstitial nephritis
- Acute pyelonephritis
- Tuberculosis
- Hematologic disorders
  - Sickle cell disease, von Willebrand disease, renal vein thrombosis, thrombocytopenia

Urinary Tract Origin

- Infection
  - Bacterial or viral, such as adenovirus
- Nephrolithiasis
- Structural/congenital anomalies
  - UPJ obstruction, hydronephrosis, vascular malformation, polycystic kidney disease
- Trauma
- Tumors
  - Renal cell carcinoma, Wilms' tumor, transitional cell carcinoma
- Exercise
- Medications
  - Aminoglycosides, amitriptyline, anticonvulsants, aspirin, chlorpromazine, coumadin, cyclophosphamide, diuretics, penicillin, thorazine

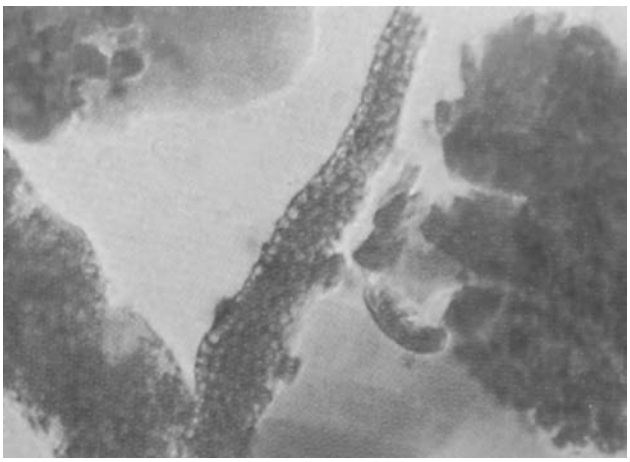

FIGURE 2.2 RBC casts. The RBCs are easily identified as biconcave discs embedded in the cast matrix. RBC casts are pathologic, and their presence is usually indicative of severe injury to the glomerulus. Occasionally, RBC casts may be seen in an individual who has been playing contact sports. The urine will usually return to normal within 24–48 hours.

RBCs may have a completely negative microscopic examination, and thus represent a false positive. Microscopic abnormal-shaped RBCs or dysmorphic RBCs are more commonly associated with nephrologic causes of hematuria, and normal-shaped or eumorphics RBCs are more commonly associated with urologic causes. The presence of proteinuria with dysmorphic RBCs further strengthens a nephrologic origin of the hematuria.[13]

Another practical test for microscopic hematuria in the outpatient clinic is a "spot" urine calcium/creatinine ratio.[14,15] If this ratio is >0.21 on two or three separate urine samples, this indicates hypercalciuria, although ratios can be significantly higher in infants.[16] Hypercalciuria does not necessarily result in nephrolithiasis but is a reported risk factor.[17] While most children with hypercalciuria do not progress to clinical nephrolithiasis,[18,19] recent reports suggest that persistent hypercalciuria may be associated with long-term bone demineralization and bone loss.[20]

It is important to note that the laboratory tests ordered for the evaluation of hematuria must be based on the clinical history and the physical examination. The physician should avoid automatically requesting tests that may be unnecessary. A panel of serum tests are selectively performed if renal and bladder sonography are negative and the urine microscopy suggests a nephrologic origin. These include CBC, basic metabolic panel, serum complement levels, antistreptolysin O (ASO) titer, and antinuclear antigen (Table 2.2). These may subsequently indicate hematologic or immunologic mediated diseases affecting the kidney.

Adrenal Mass

With the increased availability and usage of imaging modalities such as computed tomography (CT) and ultrasound, the incidence of incidentally discovered adrenal masses is increasing, in both adults and children.[21] While the vast majority of these lesions are benign and nonfunctioning lipomas or adenomas, it is incumbent upon the treating urologist to rule out a biologically active lesion through careful history and directed laboratory analysis. Unlike the adult population, the vast majority of incidentally discovered adrenal lesions are found in children already known to have medical adrenal disease, most commonly congenital adrenal hyperplasia (CAH).[22] Therefore, a newly discovered adrenal lesion should prompt a more thorough clinical investigation for risk factors for adrenal disease, including history of hypospadias or ambiguous genitalia, as well as a detailed family history of any relations with adrenal or renal lesions.

In lesions larger than 1 cm, a basic laboratory screening for biologically active lesions is indicated. Generally, this includes serum electrolytes, measurement of cortisol levels, and screening for pheochromocytoma. Screening for

TABLE 2.2 Serum panel for nephrologic hematuria

- CBC
- Basic metabolic panel
- C3 complement level
- Antistreptolysin O (ASO) titer
- Antinuclear antibodies (ANAs)

sex hormone secretion is not recommended in the absence of clinical signs of androgen or estrogen excess. Cortisol levels can be measured by a 24-hour urine free cortisol test, a late-night salivary cortisol measurement, or a low-dose dexamethasone suppression test.[21] In patients weighing greater than 40 kg, a 1 mg dose of dexamethasone is given at 11:00 p.m. and the serum cortisol measured the following morning between 8:00 and 9:00 a.m. In patients weighing less than 40 kg, the dose is adjusted to 30 μg/kg.[23] Screening for pheochromocytoma can be performed using either plasma or urinary metanephrines.[21]

Patients with abnormal screening results require further confirmatory testing prior to the diagnosis of a functioning adrenal lesion. In patients with hypertension or low serum potassium levels, the ratio of plasma aldosterone to renin should be measured. A ratio of greater than 20 with an overall aldosterone concentration of at least 15 ng/mL is diagnostic of an aldosterone-secreting lesion. Similarly, abnormalities of two of the three available screening tests for cortisol secretion are considered sufficient for diagnosis of a cortisol-secreting lesion. Either plasma or urinary metanephrines above the reference range are considered diagnostic for pheochromocytoma, but confirmatory testing is generally recommended. Biologically active lesions should generally be considered for surgical intervention.[21]

Testicular Mass

A child presenting with a testicular mass should have testicular tumor markers obtained. These include alpha-fetoprotein (AFP), human chorionic gonadotropin (HCG), lactate dehydrogenase (LDH), and placental alkaline phosphatase (PLAP). These can be checked in the outpatient office setting or may be obtained in the operating room during the placement of the intravenous lines. These levels are important for staging, as well as monitoring progress during treatment.

A serum AFP level will be elevated in tumors containing yolk sac elements, which are the most common malignant germ cell tumor in prepubertal children, and commonly seen in nonseminomatous germ cell tumor in postopubertal males. It will not be present in histologically pure choriocarcinoma or seminoma. Of note, AFP at birth is relatively high and will remain so for the first several months of life, due to the yolk sac elements present during gestation (Table 2.3).[24] Additionally, AFP can be produced by the liver, pancreas, stomach, and lung; consequently, it may be elevated in diseases of these organs. In addition to ascertaining levels of tumor markers for testicular tumors, it is helpful to check liver function tests, as an elevation in these could indicate metastatic disease to the liver, which may or may not be visible on imaging.

TABLE 2.3 Average normal serum alpha-fetoprotein of infants

Age	Mean ± SD (ng/mL)
Premature	134,734 ± 41,444
Newborn	48,406 ± 34,718
Newborn–2 weeks	33,113 ± 32,503
Newborn–1 month	9,452 ± 12,610
2 weeks–1 month	2,654 ± 3,080
2 months	323 ± 278
3 months	88 ± 87
4 months	74 ± 56
5 months	46.5 ± 19
6 months	12.5 ± 9.8
7 months	9.7 ± 7.1
8 months	8.5 ± 5.5

Nephrolithiasis

The prevalence of nephrolithiasis in children is much smaller than in the adult population,[25] and extensive laboratory assessment is recommended upon initial presentation. As opposed to the adult patient, nephrolithiasis in the pediatric population is more likely attributable to a metabolic abnormality. In the office, a urine dipstick can be performed to measure the urine specific gravity and pH. Microscopic examination of the spun urine can be performed to assess for RBCs and urinary crystals.[26,27] Calcium oxalate dihydrate crystals are seen as colorless squares with intersecting lines (resembling an envelope) (Figure 2.3). Calcium oxalate monohydrate crystals vary in size and may have a spindle, oval, or dumbbell shape. Most commonly, they appear as flat, elongated, six-sided "fence picket" crystals. Triple-phosphate (struvite and magnesium ammonium phosphate) crystals usually appear as colorless, prism-like "coffin lids" (Figure 2.4). Uric acid crystals may appear as yellow to brown rhombic plates, needles, or rosettes, and cystine crystals have a characteristic hexagonal appearance (Figure 2.5).

Standard metabolic evaluation for pediatric nephrolithiasis includes serum tests and a 24-hour urine study (Table 2.4). A serum CBC, electrolytes, bicarbonate, calcium, phosphorus, BUN, creatinine, alkaline phosphatase, magnesium, and uric acid should be obtained.

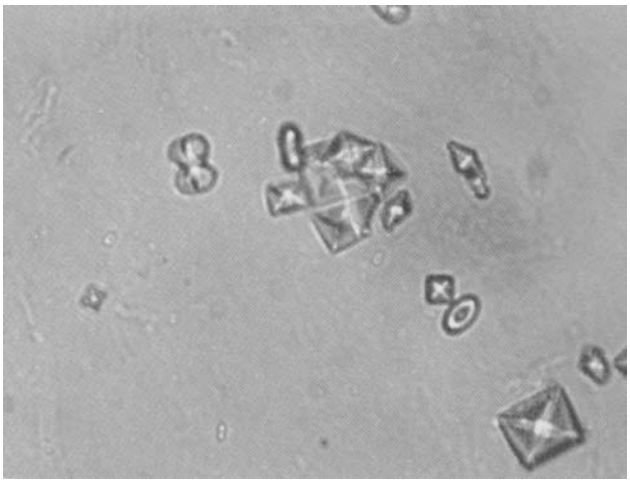

FIGURE 2.3 Calcium oxalate crystals. Calcium oxalate crystals most frequently have an "envelope" shape and appear in acid, neutral, or slightly alkaline urine.

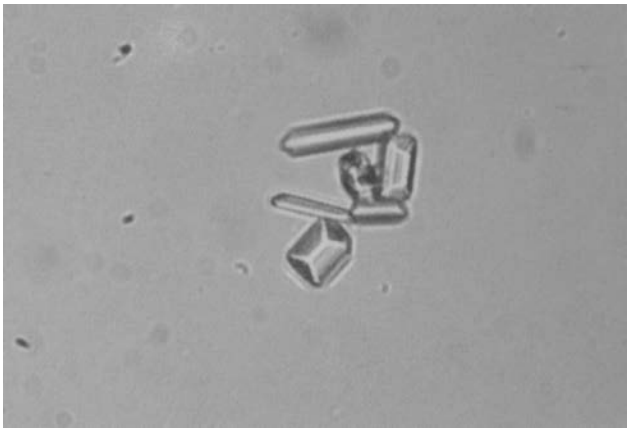

FIGURE 2.4 Triple-phosphate crystals. These crystals are common in urine sediment. Triple-phosphate crystals have a "coffin-lid" shape, are colorless, and appear in alkaline urine. These crystals may be found with struvite or magnesium ammonium phosphate stones.

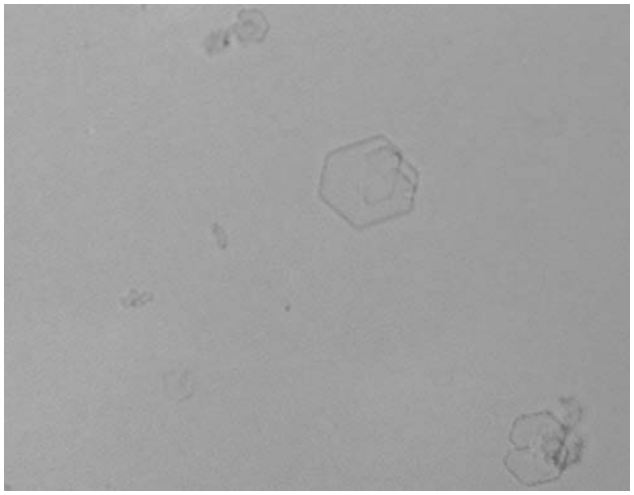

FIGURE 2.5 Cystine crystals. Cystine crystals are thin, hexagonal-shaped (six-sided) structures and appear in the urine of children with cystinuria.

TABLE 2.4 Metabolic evaluation of pediatric nephrolithiasis

Serum	Urine—24 Hour
• CBC • Basic metabolic panel • Uric acid • Calcium • Magnesium • Phosphorus • Alkaline phosphatase	• Volume • Calcium • Oxalate • Citrate • Phosphorus • Magnesium • Sodium • Uric acid • Cysteine

Elevated serum calcium suggests the possibility of hyperparathyroidism, and a serum intact parathyroid hormone level should be checked. A 24-hour urine collection should be obtained on a regular diet, to check calcium, phosphorus, magnesium, oxalate, sodium, uric acid, citrate, cysteine, creatinine, and volume.[25] The most common abnormalities seen on the 24-hour urine collection are diminished urinary volume indicative of poor hydration, hypocitraturia, and hypercalciuria.[28–31]

Intersex

The first laboratory tests ordered after a careful history and physical examination should be electrolyte assessment, a karyotype, and serum 17-hydroxyprogesterone (17-OH progesterone) levels. Obtaining electrolytes is important to identify any metabolic imbalances, such as the "salt wasting" seen in CAH that would require prompt intervention. Serum 17-OH progesterone is obtained early because elevated levels identify CAH, which is the most common intersex condition. Formerly, the child's karyotype was obtained by a buccal smear, but now it is obtained by chromosome analysis of peripheral blood lymphocytes. A fluorescent in situ hybridization (FISH) analysis may be done in conjunction with the chromosome analysis for rapid evaluation of sex chromosome presence. Although the FISH results will yield a karyotype within 24 hours, these results need verification from the formal chromosome analysis, which takes 2–3 days. Further testing will then be directed accordingly.[32,33] (See Chapter 72.)

Cryptorchidism

Nonpalpable testis in association with hypospadias requires an intersex workup. Unilateral nonpalpable testis in the presence of normal external genitalia does not require additional laboratory investigation, although a newborn with bilateral nonpalpable testes and normal male genitalia must be evaluated for female pseudohermaphroditism due to CAH. Determination of the presence or absence of the unilateral undescended testicle is accomplished via surgical exploration or diagnostic laparoscopy. In the case of bilateral, nonpalpable undescended testes in an older child, further laboratory assessment can be done to ascertain the presence of testicular tissue.

A karyotype should be performed as well as measurement of serum testosterone in cases of bilateral, nonpalpable cryptorchidism. Additionally, the serum gonadotropins, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) can be measured, and if these are elevated in the face of low testosterone, this is suggestive of anorchia.[34] It is important to note that serum testosterone is normally elevated during infancy in the neonate, at 2–3 months of age, as well as at puberty. Subsequently, serum testosterone can be measured in the neonate or during this natural surge of infancy. If this window of opportunity is missed or if evaluation is being done in the newborn period, then either an HCG stimulation test may be obtained or a measurement of serum Müllerian inhibiting substance (MIS).

Serum MIS levels produced by the Sertoli cell are the most sensitive indicator of testicular presence,[35–37] but unfortunately, the enzyme-linked immunosorbent assays (ELISAs) are not readily available in many centers. Subsequently, an HCG stimulation test is more frequently obtained. Several methods of HCG stimulation have been described.[38,39] One method is to administer HCG

intramuscularly (100 IU/kg or 5000 IU/1.7 m^2) one time and measure serum testosterone and dihydrotestosterone 72 and 96 hours later.[38] Another method involves three intramuscular injections of HCG on successive days at a daily dose dependent on their age (≤1 year old, 500 units; 1–10 years, 1000 units; ≥10 years, 1500 units).[39] The HCG should stimulate testicular Leydig cells, if present, to produce testosterone, resulting in a level of >200 ng/dL. If there is an appropriate increase in testosterone, then some functioning testicular tissue is present. If there is no response to HCG, then presumably the child is anorchid. However, there also exists the possibility of Leydig cell dysfunction, in that the Leydig cells do not respond appropriately to HCG. For this reason, many pediatric urologists still perform exploratory surgery, regardless of laboratory results.

Nocturnal Enuresis

Screening tests for nocturnal enuresis are necessary to rule out any organic etiology.[40] These include a urinalysis or urine dipstick to assess the urine specific gravity and the presence of glucose. If the specific gravity on the urinalysis is low, correlating to dilute urine, it suggests the possibility of diabetes insipidus (DI). If the urinalysis or urine dipstick demonstrates large amounts of glucose, this suggests diabetes mellitus may be present. Subsequent workup and testing can then be tailored accordingly.

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CHAPTER 3

Fetal Urology and Prenatal Diagnosis

Joao Luiz Pippi Salle and Rodrigo L. P. Romao

INTRODUCTION

Since the introduction of antenatal ultrasonography in the 1970s, the number of pregnancies with a diagnosis of a urological malformation has systematically increased. Currently, the vast majority of pregnant women worldwide will undergo at least one prenatal ultrasonography (US) scan. Despite the existing evidence that an early prenatal US improves detection of multiple pregnancies and gestation dating, antenatal detection of congenital anomalies has not translated into improved perinatal mortality and major morbidity rates.[1] Nevertheless, the high sensitivity of urological anomaly detection (around 90%) has impacted significantly the practice of pediatric urology as a specialty.[2] The scope of practice has shifted from a primarily interventional/surgical model directed at symptomatic patients to a counseling role for those who are often asymptomatic and with problems of variable clinical significance.[3,4]

Antenatal hydronephrosis is seen in 1%–5% of all pregnancies and represents the most frequent prenatal diagnosis overall, with the majority of patients depicting mild, non-specific dilation of the renal pelvis that will resolve spontaneously.[3,5] Detection of this "abnormality" in the fetus is a source of parental anxiety and triggers requests for specialized consultation. Many of these babies have no significant urological pathology and become known colloquially as "VOMITS" (victims of modern imaging technology). Pediatric urologists are often called to contribute in the prenatal evaluation and management of these patients and in many cases will carry on taking care of them for many years postnatally. A comprehensive consideration of the postnatal investigation and management of the various anomalies detected by prenatal ultrasonography is detailed in the relevant chapters elsewhere in this book. This chapter will therefore focus predominantly on the following areas of fetal and perinatal urology:

- Pathophysiology of urinary tract malformations
- Current status of fetal intervention
- Recommendations for prenatal counseling/delivery
- Pre- and post-natal findings of the most commonly detected anomalies
- A rational approach to early postnatal investigation and management, specifically following a diagnosis of antenatal hydronephrosis
- Significance of mild dilatation ("pelviectasis")

FUNCTIONAL DEVELOPMENT OF THE URINARY TRACT

Detailed embryology is beyond the scope of this chapter, and is covered elsewhere. A pivotal event in functional development occurs at around 32 days of gestation when the ureteric bud fuses with the metanephric mesenchyme to initiate the formation of excretory nephrons. Nephrogenesis proceeds by a process of reciprocal induction until the 36th week of pregnancy, with the glomeruli, proximal tubules, and loops of Henle being derived from the metanephros, whereas the collecting ducts, calyces, and renal pelves are derivatives of the ureteric bud. In man, nephrogenesis ceases at 36 weeks, and thereafter the number of nephrons remains fixed at between 0.7 and 1 million per kidney. Major developmental defects dating from the first trimester of gestation are characterized by agenesis or dysplasia (arrested differentiation that is characterized histologically by immature tubules and the presence of aberrant mesenchymal derivatives such as smooth muscle and cartilage).

URINE PRODUCTION AND EXCRETORY FUNCTION

The primitive nephrons begin to excrete urine at around the 9th week of gestation. Initially, its composition resembles an ultrafiltrate of plasma, but as gestation progresses and tubular function matures, fetal urine begins to acquire the low electrolyte, high creatinine composition that characterizes normal urine in postnatal life.[6] Fetal urinary output at different stages in gestation has been documented by ultrasonography of the fetal bladder in healthy fetuses. By the third trimester, the hourly fetal urine production is as high as 30–40 mL/h and it constitutes around 90% of the amniotic fluid[7] (Figure 3.1). In the fetus the role of the kidney lies principally in fluid excretion, since homeostatic regulation of extracellular fluid composition is undertaken by the placenta. For this reason, creatinine clearance does not provide a meaningful measure of fetal renal function. However, extrapolation of values derived from iothalamate studies in the fetal lamb suggest that the fetal glomerular filtration rate (GFR) at 36 weeks of gestation approximates to only 5% of the surface corrected adult value.[8]

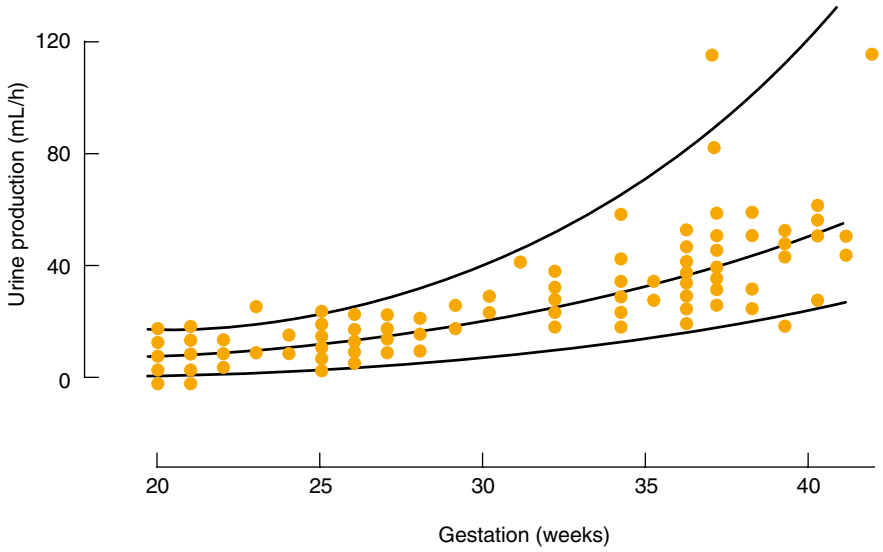


FIGURE 3.1 Fetal urine production at difference stages in normal pregnancy. (Adapted from Rabinowitz R et al. *YMOB* 1989;161(5):1264–6.)

THE KIDNEY LUNG LOOP

Amniotic fluid, of which fetal urine is the major constituent, has long been recognized as playing a critical role in lung development, and reduced amniotic fluid (oligohydramnios) is associated with varying degrees of pulmonary hypoplasia depending upon the timing and severity of the reduction in fetal urinary output. The question whether amniotic fluid plays merely a mechanical role in lung development (supported by the observation that amnioinfusion with normal saline or ringer's solution may improve pulmonary hypoplasia, especially in patients with premature rupture of membranes[9,10]) or is the vehicle for active renal-derived growth factors or other active agents remains unanswered. Severe pulmonary hypoplasia associated with bilateral renal agenesis (Potter's Syndrome) and prolonged oligohydramnios is characterized by a decrease in lung size and cell number, narrow airways, retardation of epithelial differentiation and surfactant deficiency. Furthermore, pulmonary hypoplasia can also occur secondary to lung growth restriction caused by compression of the chest cavity in the absence of amniotic fluid.[11]

CHANGES AT THE TIME OF BIRTH

In the latter stages of pregnancy the fetus maintains a physiologic state of volume expansion. A high fluid intake of swallowed amniotic fluid is matched by a high obligatory urine output. If a comparable diuresis was maintained after birth, dehydration and volume depletion would rapidly supervene, but at the time of delivery, renal physiology rapidly switches to a fluid-restrictive mode, prompted in part by high circulating levels of aldosterone, vasopressin, and catecholamines. In addition, parenchymal perfusion and GFR increase dramatically in response to a fall in peripheral renovascular resistance and greatly increased renal perfusion. But, despite these adaptive changes, renal function remains marginal, with a corrected GFR at birth averaging only 30 mL/1.73 m^2. It is not until 2 years of age that GFR reaches the normal surface corrected adult value of approximately 125 mL/1.73 m^2.

PATHOPHYSIOLOGY OF FETAL UROPATHY

Traditionally, fetal uropathy has been divided into: problems with a clear genetic background (autosomal recessive polycystic kidney disease), problems associated with defective nephrogenesis (renal agenesis, dysplasia, etc.), fetal upper and lower urinary tract obstruction and vesicoureteral reflux (VUR).

Defective Nephrogenesis

Experimental ablation of the mesonephric duct (the origin of the ureteric bud) results in ipsilateral renal agenesis.

Renal dysplasia can be caused by a number of different mechanisms, including defective interaction between the ureteric bud and metanephric mesenchyme, intrinsic defects of differentiation, and a variety of extrinsic insults, notably obstruction. The classic observational studies of Mackie and Stephens[12] demonstrated the association between ureteral ectopia, faulty induction of nephrogenesis, and renal dysplasia in duplex systems. This "ureteric bud hypothesis" can also be invoked to explain the association between renal dysplasia and high-grade reflux associated with ureteric ectopia.

In recent years, the understanding that defective nephrogenesis (i.e. renal "dysplasia") and obstruction/VUR often coexist without necessarily having a cause-effect relationship have led to the development of the terminology CAKUT—congenital anomalies of the kidney and urinary tract. CAKUT encompasses renal agenesis, hypoplasia, dysplasia, multicystic kidney dysplasia, duplication of the collecting system, ureteropelvic junction obstruction (UPJO), megaureters, posterior urethral valves (PUV)

and VUR. The incidence of CAKUT is 1/500 live births and the incidence of neonatal death caused by CAKUT is around 1/2000 live births.[13,14] The possible role for a genetic cause is supported by the observation that in about 10% of CAKUT patients, renal abnormalities are found in close relatives, albeit with great clinical variability. However, despite the identification of numerous molecular mechanisms associated with CAKUT (mutations on HNF1β, PAX2[15] and the recently described RET signaling disruption,[16] to name a few), no classical Mendelian patterns of inheritance have been demonstrated and significant modifying environmental factors are likely to play a role in the disease development process.[13]

Fetal Urinary Tract Obstruction

Upper Tract

Experimentally, even brief periods of obstruction during nephrogenesis have been shown to induce apoptosis, aberrations of cell proliferation, and trans-differentiation of mesenchyme into the phenotypes that characterize renal dysplasia. Gene expression is also disrupted by obstruction.[17] However, the results of experimentally created obstruction in animal models must be interpreted with some caution in view of the difficulty in reproducing a model of chronic, partial upper tract obstruction—the pattern most commonly encountered in clinical practice.

Lower Tract: Bladder Outlet Obstruction

Experimentally induced infravesical obstruction was extensively studied by Harrison and his colleagues in San Francisco in the 1980s.[18] For example, these authors induced partial urethral obstruction in fetal lambs at 93–107 days of gestation. They then showed that the hydronephrosis, urinary ascites, and fetal pulmonary hypoplasia, which ensued in untreated fetal lambs was reversed when the obstructed bladder was subsequently decompressed in utero. These and other studies underpinned the scientific rationale for introducing intrauterine bladder drainage in clinical practice. Unfortunately, subsequent experience with fetal intervention in the clinical setting suggests that some of the findings in the fetal lamb model may not translate to man. The current status of fetal intervention is considered in more detail below.

Fetal Vesicoureteral Reflux

The pattern of severe damage associated with grade V reflux can reasonably be ascribed to dysplasia resulting from a ureteric bud defect. By contrast, kidneys exposed to mild or moderate reflux in utero often appear normal or show global reduction in size with smooth outlines (hypoplasia) on technetium 99m (^{99m}Tc) dimercaptosuccinic acid (DMSA) imaging. Focal scarring is predominantly a feature of postnatal infection.[19]

Very little is known of the mechanisms of renal damage seen in conjunction with sterile fetal reflux but in one fetal lamb model, experimentally induced VUR has been shown to exert significant changes on tubular function and on postnatal DMSA appearances of the kidneys.[20] In addition, clinical evidence is accumulating to indicate that, even in the absence of infection, high-grade bilateral primary reflux in males carries a greater risk of renal impairment than was previously recognized.[21] While the 'water hammer' effect of sterile urine has been largely discounted as a cause of ongoing postnatal renal damage, this mechanism may exert a more significant impact in the fetus, possibly associated with high voiding pressures seen physiologically in male infants.[22]

CLINICAL SITUATIONS THAT MAY REQUIRE PRENATAL INTERVENTION

The only scenario in the realm of urology directly amenable to fetal intervention is lower urinary tract obstruction (LUTO) in males. Fetal intervention for spina bifida also has the potential to affect long-term urological outcomes and will thus be briefly discussed.

Infra-Vesical Obstruction (LUTO) in Males

It is portrayed antenatally by bilateral hydroureteronephrosis, megacystis/thick-walled bladder and a dilated posterior urethra (keyhole sign—Figures 3.2–3.4) and is most commonly caused by posterior urethral valves (PUV), although other rarer diagnoses, such as urethral atresia, prune-belly syndrome and congenital megalourethra[23] can produce similar sonographic findings (Figures 3.5 and 3.6). Megacystis can be observed as early as the first trimester of pregnancy, when it is defined by a bladder diameter >6 mm; half of the patients with early detection of megacystis will undergo spontaneous resolution. In the second trimester, megacystis is defined as an abnormally distended bladder and some authors take into account bladder emptying, defining failure to empty after 45 minutes of observation. When faced with a fetus with persistent megacystis, besides assessing the remainder of

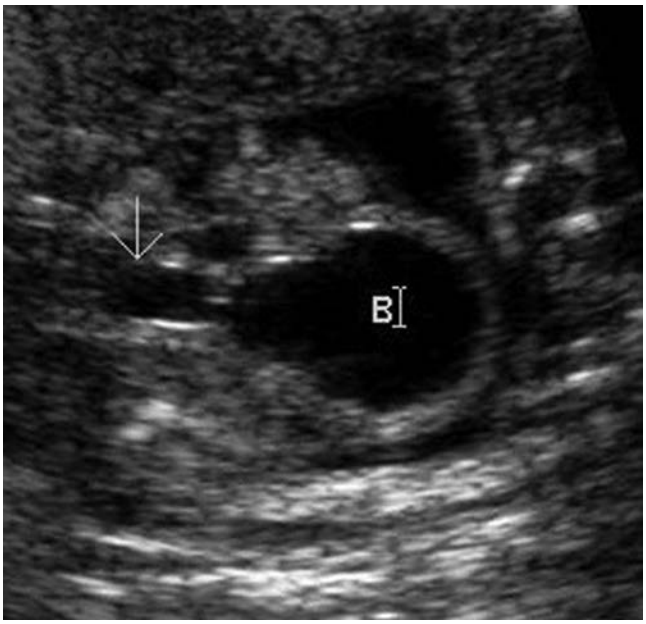


FIGURE 3.2 Keyhole sign detected early in pregnancy; "B" represents the bladder and the arrow points to the dilated urethra.

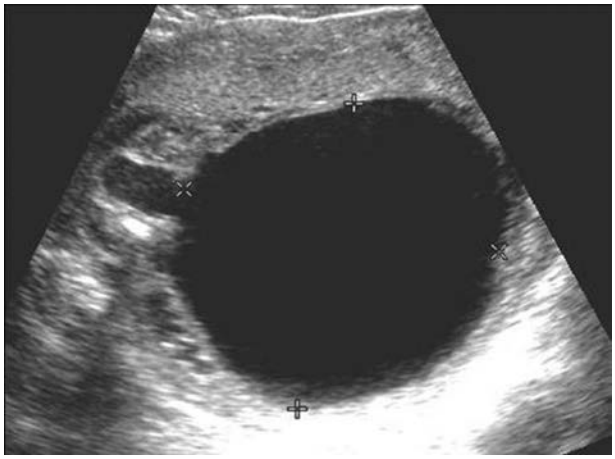


FIGURE 3.3 Megacystis associated with keyhole sign in a fetus with anhydramnios.

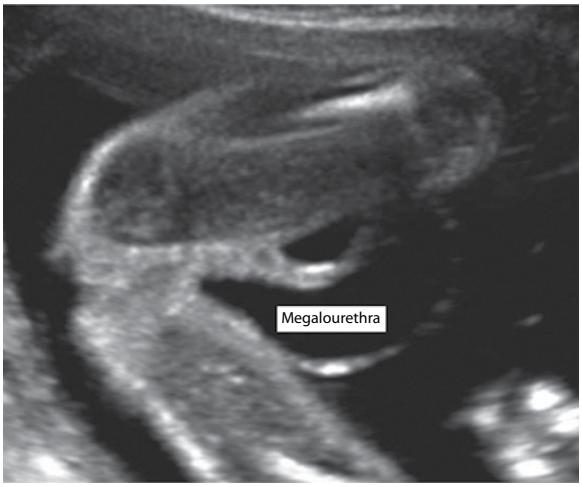


FIGURE 3.5 Prenatal sonographic appearance of congenital megalourethra.

the urinary tract for the aforementioned abnormalities associated with infra-vesical obstruction, the parents have to be advised about an increased risk for aneuploidy (as high as 25%) and associated anomalies (33%—most commonly trisomy 13 or 18). For this reason, some fetal specialists offer amniocentesis in this situation.[24] Megacystis can also be seen in the setting of megacystis-microcolon intestinal hypoperistalsis syndrome (MMIHS), a rare bowel and bladder motility disorder that affects predominantly females. Diagnosis is suggested prenatally by the association of megacystis and polyhydramnios. Patients are almost uniformly dependent on parenteral nutrition to survive and a recent literature review reported an overall survival rate just below 20%[25] (Figure 3.7).

The combination of early (<24 weeks) detection of megacystis with severe, often bilateral hydronephrosis (AP diameter >10 mm before 24 weeks of gestation), abnormal appearance of the renal parenchyma (cortical cysts, increased echogenicity) and oligohydramnios has been used as a surrogate of impaired renal function/severe infra-vesical obstruction, which will ultimately lead to pulmonary hypoplasia and fetal/neonatal demise (see Figure 3.3—massive megacystis and keyhole sign with anhydramnios). Therefore, antenatal intervention for LUTO has historically been offered to this high risk male population without evidence of other severe congenital or chromosomal anomalies.[26] An attempt has been made to correlate levels of urinary markers obtained by fetal vesicocentesis, such as sodium, calcium and β2-microglobulin with the degree of underlying renal impairment, and thus predict which patients would have a better chance of attaining acceptable renal function following prenatal relief of the obstructive component.[27] Urinary sodium > 100 mEq/L and calcium > 1.2 mmol/L appear to be the most accurate markers linked to worse renal outcomes. However, a systematic review demonstrated that none of the markers described can accurately predict poor postnatal renal function and reference values (especially for β2-microglobulin) have to be interpreted taking into account the gestational age since there is a wide variation due to changes in renal physiology.[28]

Initially, bladder decompression was achieved through open surgery, however modalities for prenatal intervention have evolved to become minimally invasive and include

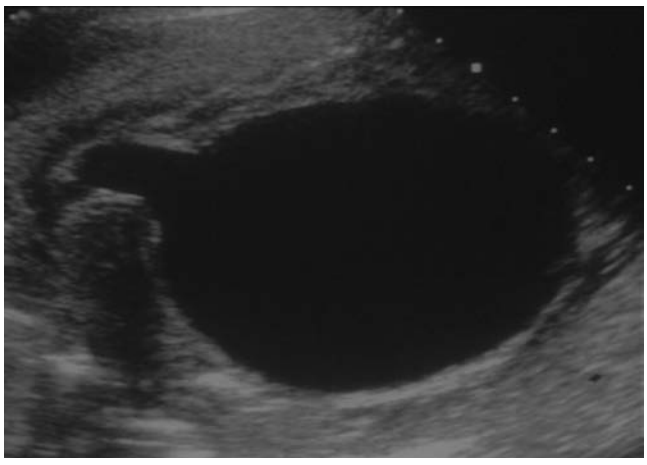


FIGURE 3.4 Megacystis and keyhole sign.

FIGURE 3.6 Postnatal appearance of infant with congenital megalourethra.

FIGURE 3.7 Megacystis associated with polyhydramnios suggesting megacystis-microcolon intestinal hypoperistalsis syndrome (MMIHS).

vesicoamniotic shunting (VAS)[29] and prenatal fetoscopic valve ablation.

VAS is the most common intervention for LUTO. It is usually performed as an outpatient procedure with maternal sedation and ultrasonography guidance. A suprapubic pigtail catheter is inserted communicating the fetal bladder with the amniotic cavity.[30,31] Dislodgement of the shunt requiring reinsertion is common[31] (Figure 3.8). Furthermore, potentially serious morbidity may arise from the procedure, such as bleeding, infection and even miscarriage (1%–2% risk).[26] Bladder and intestine herniation through a widened puncture site have been observed (Figures 3.9–3.11). Alternatively, serial infusion of normal saline or ringer's lactate in the amniotic cavity can prevent the development of pulmonary hypoplasia; this procedure, known as amnioinfusion, has been scarcely described in patients with LUTO[9] but its use is well established for

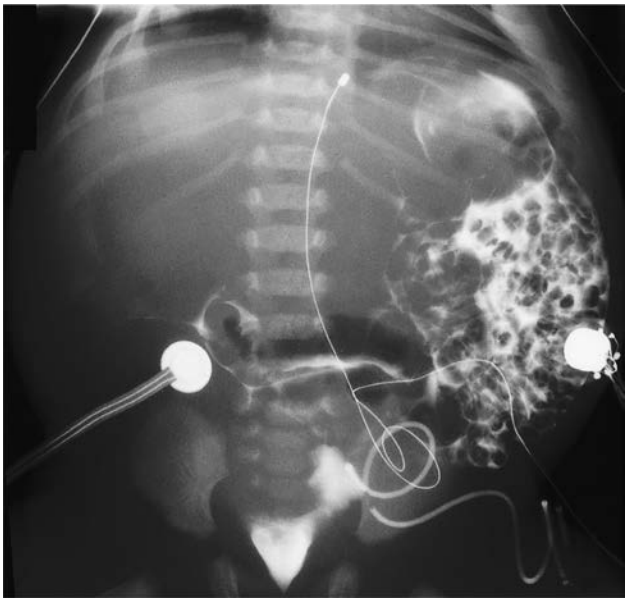


FIGURE 3.8 Complication of vesicoamniotic shunting. A postnatal contrast study reveals intraperitoneal placement of shunt with extravasation of contrast and urinary ascites. Despite shunting, this neonate succumbed to pulmonary hypoplasia.

FIGURE 3.9 Newborn with herniated bowel and vesico-amniotic shunt following antenatal intervention.

FIGURE 3.10 Newborn with prolapsed bladder following antenatal intervention.

FIGURE 3.11 Detail of prolapsed bladder following antenatal intervention.

allowing adequate lung development in patients with premature rupture of membranes.[10]

In recent years, fetal cystoscopy has been introduced as both a diagnostic and therapeutic tool in pregnancies complicated by LUTO.[32,33] It offers the advantage of allowing differentiation between PUV and urethral atresia as well as prenatal ablation of the former.[34] Notwithstanding the theoretical benefit of performing a definitive intervention with full visualization of the anatomy, a systematic review failed to demonstrate improved perinatal mortality/morbidity compared to VAS, called attention to the low quality of the reports on the subject and regarded fetal cystoscopy as "experimental" at this stage.[35]

In contrast to the evidence-based approach developed by Harrison's group in San Francisco, obstetricians in many other centers enthusiastically adopted fetal intervention on an uncritical and unreported basis in the 1980s. Where results were published, they were uniformly disappointing. The Fetal Surgery Register[36] reported an overall mortality rate of 59% in 73 fetuses—but this was probably an overoptimistic assessment, since an accurate urologic diagnosis was not established in many cases. By the end of the 1980s, enthusiasm for fetal intervention was waning. Mandell et al.[37] identified 24 related publications between 1982 and 1985, but only 7 publications between 1985 and 1989, of which two were single case reports. Medium to long-term outcome results have been reported by some centers, which continue to undertake fetal intervention on a responsible and audited basis. In Detroit, Freedman and associates[38] documented the outcome of vesico-amniotic shunting in 34 fetuses treated during the period 1987–1996. Of these, only 17 survived to term, of whom 14 were assessed after 2 years minimum follow-up. Eight of these 14 children had already progressed into end-stage renal failure and 5 had been transplanted at the time of the study. Thus, of the original total of 34 shunted fetuses, only 6 were alive with normal renal function when assessed after 2 years of age. In another long-term study, the San Francisco group[39] analyzed the late outcome of 36 fetuses treated in the period 1981–1999. All had been selected for treatment on the basis of favorable urinary biochemistry. Of the 36 treated fetuses, 14 had a diagnosis of posterior urethral valves—of whom 6 did not survive to term. However, 8 infants with prenatally detected urethral valves treated in utero did survive and were evaluated at the mean of 11.6 years—when 5 were in renal failure. In all, only 3 (21%) of the 14 fetuses with posterior urethral valves survived with normal renal function. Biard et al. reported the outcomes of 20 pregnancies with LUTO treated with VAS and followed for a mean of 5.8 years; despite the high survival rate (91%) and the findings that children were neurodevelopmentally normal and scored similar to controls in health-related quality of life questionnaires, 1/3 of the patients required renal replacement therapy (dialysis and/or transplantation) and roughly 40% intermittent catheterization for bladder management.[40] In the authors' institution, long-term follow-up data was available for 6 patients from a total of 14 who underwent VAS in the last 20 years; after a mean follow-up of 10.8 years, 3 patients had undergone renal transplantation, 1 was on renal replacement therapy and 1 was being prepared for preemptive transplantation (unpublished data). From a meta-analysis of published series totaling 342 fetuses, Clark et al.[41] concluded that "amongst controlled studies bladder drainage appeared to improve perinatal survival relative to no drainage." Nevertheless, these authors cautioned that this positive conclusion might be influenced by a subgroup of fetuses with poor prognosis who had experienced a particular benefit in terms of early survival.

In summary, if survival is taken as the endpoint, there is reasonable evidence that intrauterine intervention ("fetal surgery") is effective, probably by facilitating lung development. Unfortunately, this does not appear to be true of renal development, since a high proportion of infants who have been treated in utero nevertheless progress rapidly into end-stage renal failure—with significant implications for their quality of survival in childhood and later life. Long–term outcome studies and a growing body of anecdotal evidence indicate that fetal intervention does have the potential to increase survival by reducing the risk of pulmonary hypoplasia. By contrast, there is very little evidence that the prognosis for renal function is significantly improved by fetal intervention—probably because this is largely determined by dysplasia, which predates diagnosis and treatment.

Indeed, it seems highly likely that some infants who might otherwise have succumbed to pulmonary hypoplasia have survived as a result of fetal intervention only to progress rapidly into end-stage renal failure in infancy or early childhood. Ransley[42] has consistently argued that our perception of fetal intervention has been colored by poor outcomes in bad prognosis cases and has suggested that the potential benefits of fetal intervention might be more apparent if it was extended to include all male fetuses with evidence of outflow obstruction in the second trimester, which is the subject of an ongoing multicentric prospective randomized trial known as PLUTO (percutaneous shunting for lower urinary tract obstruction). This trial is not based on strict entry criteria but rather on the "uncertainty" principle, i.e. whenever the clinical team is significantly uncertain as to whether a male fetus with evidence of isolated bladder outflow obstruction should be shunted or not, the fetus is eligible for randomization. Furthermore, fetuses that are not randomized (either shunted or not) will be entered into a prospective registry that will allow comparison of outcomes later on. The trial predicts enrollment of 200 pregnancies (100 for each arm) and the primary outcomes are perinatal mortality and renal function at 4–6 weeks and 12 weeks of age.[30]

Finally, it is not uncommon for termination of pregnancy (TOP) to be offered to families in light of detection of LUTO associated with oligohydramnios or findings suggestive of severe bilateral renal impairment and the perspective of need for lifelong renal replacement therapy and its associated morbidity. In a multicentric European study analyzing over 700,000 births, renal malformations were diagnosed prenatally in 82% of all cases and 29% of those pregnancies were terminated.[43] In a similar study from the US targeting a population of 163,000 pregnant women, the TOP rate for PUV was 46%.[44] Nonetheless, it should be kept in mind that there is no single predictive factor with enough specificity to foresee which patients will truly have a poor renal outcome postnatally and thus support TOP, as illustrated by a study that followed 10 fetuses for whom TOP was offered based on sonographic

findings and declined; 5 died in the first month of life and all 5 survivors (2 of which had oligohydramnios) had a normal creatinine and variable degrees of proteinuria after a median follow-up of 29 months.[14]

Spina Bifida

A recently conducted randomized trial concluded that prenatal myelomeningocele repair through open fetal surgery results in improved motor outcomes and reduced need for ventriculo-peritoneal shunt placement, whilst with an increased risk of preterm delivery and maternal morbidity.[45] However, after a mean follow-up of 9.6 years, no difference was found in terms of management of the neurogenic bladder and bowel in patients who underwent fetal surgery compared to controls.[46]

CLINICAL SITUATIONS THAT WARRANT PRENATAL COUNSELING, DELIVERY IN A TERTIARY CARE CENTER AND PROMPT POSTNATAL EVALUATION, BUT NOT PRENATAL INTERVENTION

The main diagnoses in this category are autosomal recessive polycystic kidney disease (ARPKD), bladder exstrophy, cloacal exstrophy and some Prune-Belly-Syndrome (PBS) patients as well as some rare females with cloacal anomalies and hydrocolpos/secondary urinary obstruction.

With an incidence between 1:10,000 and 1:40,000 and a variable phenotype, ARPKD can be diagnosed prenatally by the findings of nephromegaly and hyperechogenicity affecting both kidneys (Figure 3.12). An empty bladder and oligohydramnios leading to Potter's Syndrome are possible, which explains the neonatal mortality rates between 30 and 50% due to respiratory insufficiency. Prenatal molecular diagnosis is now available,[47] which is key especially in cases of perinatal demise for the purpose of parental counseling, since the risk of recurrence is 25%. No prenatal intervention is available, however delivery in a tertiary care center is mandatory for advanced respiratory care as well as renal replacement therapy, which can be required as soon as the neonatal period.

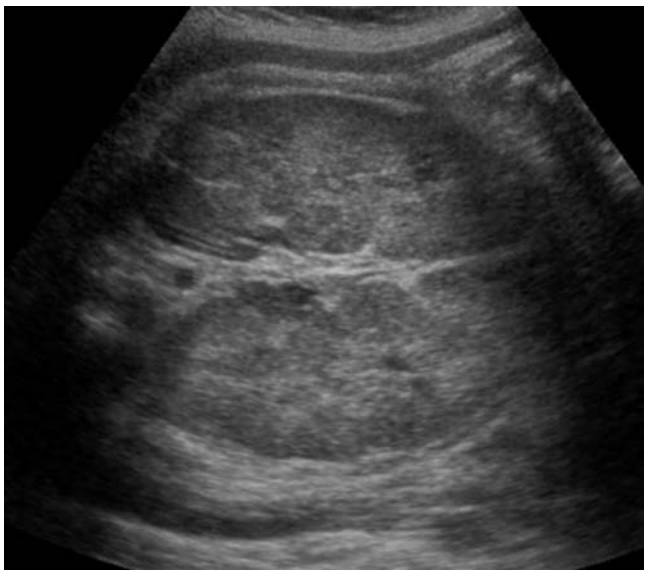


FIGURE 3.12 Enlarged, hyperechogenic kidneys at 36 weeks' gestation suggestive of ARPKD.

Antenatal detection of bladder and cloacal exstrophy can be very challenging. In a report by one of the only two centers treating these conditions in the UK, only 25% of the patients were diagnosed prenatally. Furthermore, the authors found that one of the patients referred with a prenatal diagnosis of bladder exstrophy was in fact born with a simple gastroschisis, highlighting the hazard of misdiagnosis with its catastrophic potential consequences (i.e. in case the parents had opted for TOP).[48]

Bladder exstrophy is suggested prenatally by 5 sonographic signs: absent bladder, lower abdominal bulge corresponding to the exstrophied bladder, small penis with anteriorly displaced scrotum, low umbilical insertion and widening of the iliac crests (Figure 3.13a and b).[49] Prenatal detection rates just over 50% are not as high as the ones observed for other urological anomalies.[43] Associated problems are uncommon. The main differential diagnosis prenatally is an abdominal wall defect, such as gastroschisis or omphalocele, however in either case a normally filled bladder should be identified within the pelvis.[24]

Cloacal exstrophy, also called OEIS complex (omphalocele, exstrophy, imperforate anus and spinal anomalies) is a severe congenital malformation and prenatal diagnosis is based on the association of anomalies; detection rates are similar to classic bladder exstrophy (just above 50%).[50] Usually, non-visualization of the bladder coupled with a large lower midline abdominal wall defect and a lumbar myelomeningocele will suggest OEIS. Associated anomalies within the CAKUT spectrum are commonly present[24,51] and patients sometimes succumb in utero to pulmonary hypoplasia secondary to oligo/anhydramnios. Differential diagnosis between OEIS and classic bladder exstrophy is not always straightforward, which is a source of significant anxiety for both parents and the medical team during discussions about continuation of pregnancy.

Occasionally, cloacal anomalies that do not fit into the full OEIS complex spectrum can be diagnosed prenatally as well. Prenatal US demonstrates a cystic structure in the pelvis that may be lobulated or contain debris, but sometimes can be mistaken for a megacystis in a female fetus or else a fetus with findings suggestive of ambiguous genitalia. The cystic structure corresponds to a hydrocolpos, which can cause severe secondary urinary obstruction.[52]

Fetal magnetic resonance imaging (MRI) holds promise as a confirmation test in the presence of equivocal sonographic findings for bladder exstrophy, OIES and cloacal anomalies. It provides enhanced soft tissue resolution and allows accurate gender determination, which is important for prenatal counseling of the bladder exstrophy spectrum conditions, since males will require more extensive surgical reconstructive work postnatally.[48,53]

Due to the wide variability of findings, PBS can present within the full-blown LUTO spectrum described before

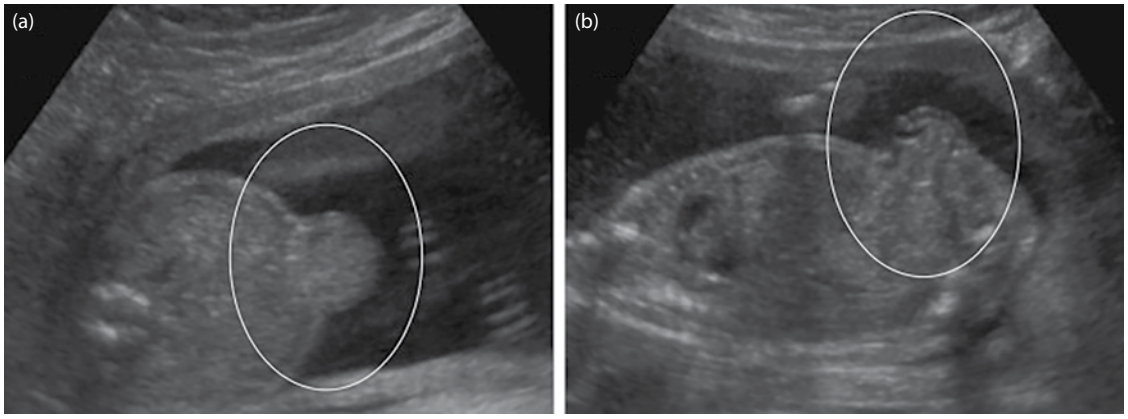


FIGURE 3.13 Prenatal ultrasound of fetus with bladder exstrophy. (a) Lower abdominal bulge is highlighted. (b) Bladder exstrophy and phallus with dorsal curvature are outlined.

or not. Possible sonographic findings are enlarged, thick-walled bladder, bilateral hydroureters with or without hydronephrosis, abnormal abdominal wall, bilateral intra-abdominal testicles and megalourethra.

Because of the inherent high complexity and potential need for medical/surgical interventions in the neonatal period, patients diagnosed with these conditions prenatally should be delivered in a tertiary care center or at the very least be transferred to one immediately after birth.

A consequence of prenatal diagnosis for these conditions, which require major reconstructive procedures and are associated with long-term morbidity, is a sharp increase in TOP rates (Figure 3.14a and b). In a review by Cromie et al., 31% and 25% of pregnancies with PBS and bladder exstrophy were terminated, respectively.[44] In an European series, 80% of bladder exstrophies detected antenatally underwent TOP.[43] Once again, the change in the scope of practice of pediatric urologists is highlighted, with more families requiring counseling and declining rates of reconstructive surgery. Particularly in the case of classic bladder exstrophy, the lack of associated anomalies and renal dysfunction, as well as the possibility of achieving reasonable quality of life with adequate postnatal care turn systematic TOP into an overly aggressive policy in

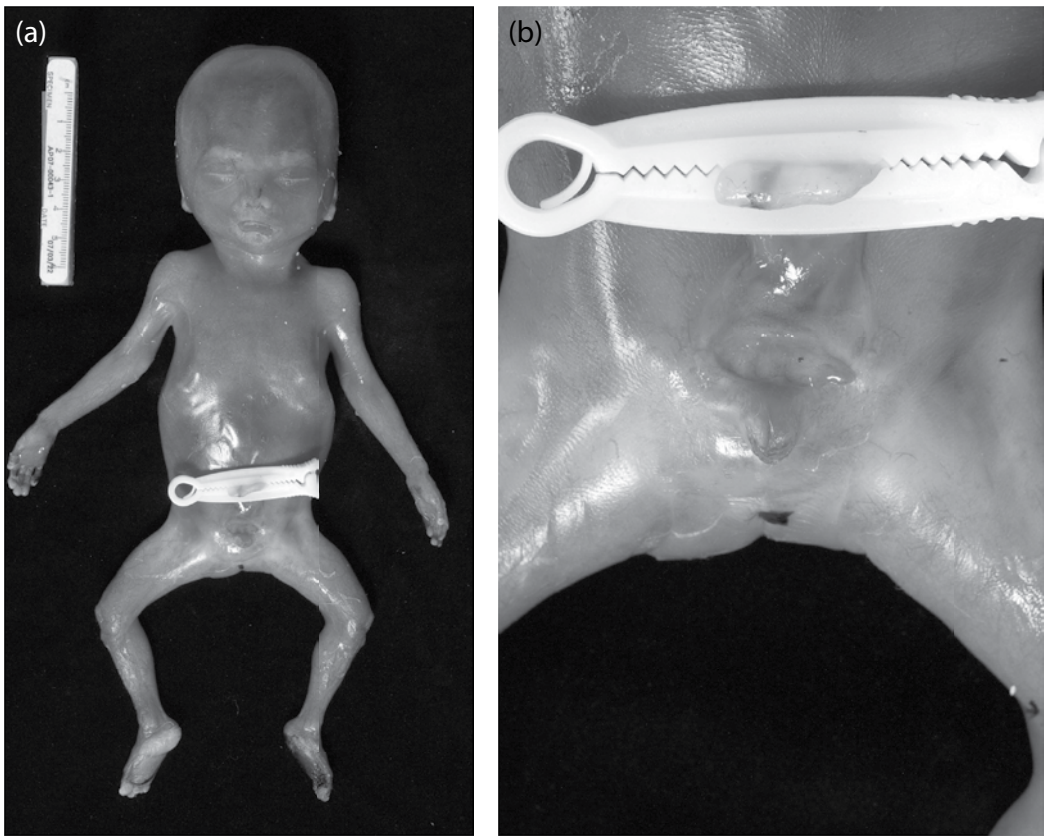


FIGURE 3.14 (a, b) Fetus with bladder exstrophy; parents opted for termination of pregnancy.

the authors' view, underlining the importance of broad and realistic prenatal advice. The importance of prenatal counseling by pediatric urologists and even other professionals experienced with the holistic management of these patients (i.e. social workers, psychologists, etc.) has to be underscored.

COMMON PRENATAL SONOGRAPHIC FINDINGS AND CORRELATION WITH POTENTIAL POSTNATAL FINAL DIAGNOSES THAT REQUIRE NON-URGENT POSTNATAL EVALUATION

The vast majority of patients diagnosed prenatally with a urological abnormality will require non-urgent postnatal consultation. This subgroup is largely represented by unilateral antenatal hydronephrosis (ANH). Ureteral dilatation, multicystic dysplastic kidney (MCDK) and duplex collecting system with its associated problems (i.e. ectopic ureter, dysplastic upper pole, ureterocele) are other conditions that fit into this category. In most situations, it will be difficult to establish a definitive diagnosis until the postnatal investigation is completed. The true benefit of prenatal diagnosis in these instances is debatable, since there is no role for intervention and a positive finding is a source of significant parental anxiety. It is challenging to determine how much information should be offered to parents, given the inherent uncertainty about postnatal outcomes. A systematic review comparing the impact of high feedback (women can see the screen and get detailed explanations about all findings) vs. low feedback (women cannot see the screen and get a brief summary at the end of the study) prenatal ultrasonography on maternal anxiety was inconclusive as to which feedback modality would improve maternal health behaviors.[54]

Dilatation of the renal pelvis (hydronephrosis) is the most common abnormality detected prenatally overall, with an incidence of 1%–5%.[5] Hydronephrosis is a sonographic finding rather than a disease per se, characterized by confluent dilatation of the collecting system; isolated dilatation of the upper urinary tract may denote active obstruction (ureteropelvic junction obstruction—UPJO) or most commonly non-obstructive, non-specific and self-resolving dilatation. Alternatively, the presence of a small kidney with minimal or no parenchyma and non-communicating cysts is highly suggestive of a multicystic dysplastic kidney (Figure 3.15). When faced with a prenatal diagnosis of hydronephrosis, the caregiver must pay attention to 2 aspects: unilateral versus bilateral dilatation and presence of other urinary tract findings. In the presence of bilateral hydronephrosis, careful consideration should be given to the lower urinary tract and the possibility of infra-vesical obstruction (see previous LUTO section). Another important aspect of sonographic evaluation is echogenicity of the renal parenchyma. Abnormally echogenic (bright) kidneys (Figure 3.16) are usually associated with dysplasia and functional compromise to variable degrees can be expected; as a parameter for comparison, echogenicity of the kidneys should be similar to that of the liver or spleen.

Quantitatively, ANH is defined based on the anteroposterior (AP) diameter of the renal pelvis, measured following a standardized method (transverse view right on the edges of the renal parenchyma to avoid overestimations by measuring the extra-renal pelvis—Figure 3.17). There is no consensus as to which measurements are clearly associated with postnatal pathology. Whereas exact cutoffs to define significant dilatation are lacking, it seems that isolated pelvis dilation <15 mm in the third trimester is hardly ever associated with postnatal pathology requiring intervention.[55] The Society for Fetal Urology (SFU) grading system is a qualitative tool used worldwide to report ANH findings as follows:

- *Grade I*: Splitting or separation of the renal pelvis (Figure 3.18)
- *Grade II*: Moderate dilatation of the renal pelvis with no calyceal dilatation (Figure 3.19)

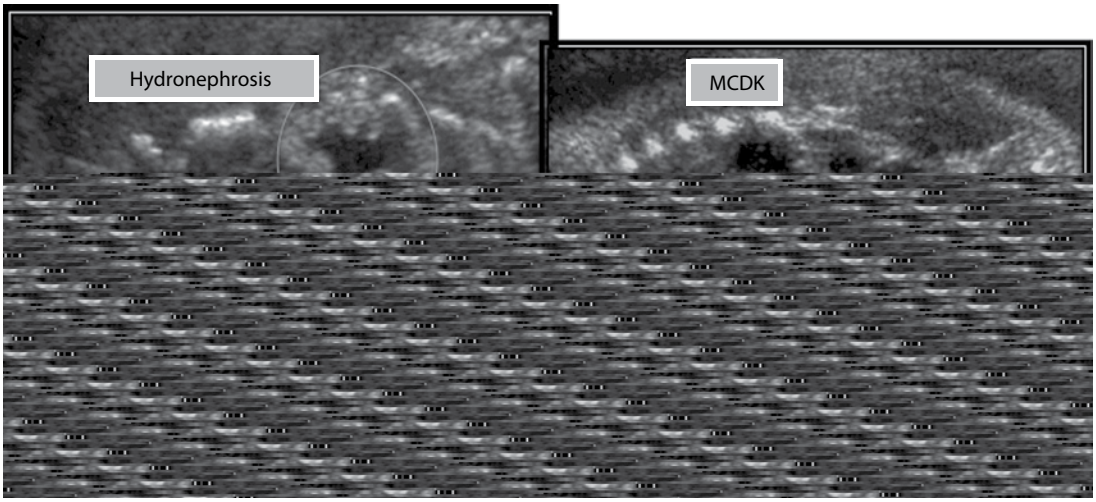


FIGURE 3.15 Comparison of hydronephrosis and multicystic dysplastic kidney appearances on prenatal ultrasound. Note that hydronephrosis is confluent whereas MCDK is characterized by non-communicating cysts.

to diagnosis and treatment becomes less invasive, there has been a shift towards being more discriminatory to request a VCUG to diagnose VUR in a patient with isolated ANH.

Both the Canadian and the American Urological Associations[62,63] guidelines recommend a VCUG for infants with antenatally detected hydronephrosis in the following scenarios:

- Isolated high-grade hydronephrosis (SFU 3-4)
- Hydroureter or bladder abnormalities on ultrasonography associated with any degree of dilatation
- After an episode of febrile UTI

Nevertheless, the SFU guidelines acknowledge that there is no evidence to support or avoid postnatal imaging for VUR[5] and the American Academy of Pediatrics has recommended against a VCUG after the first episode of febrile UTI in infants on their latest guidelines.[64] Although comprised mostly of case series with variable radiological criteria, the best available evidence is the meta-analysis by Lee et al. (1308 subjects), which demonstrated that the risk of any postnatal pathology increased with the grade of antenatal hydronephrosis from 11% for mild to 88% in severe cases, EXCEPT for VUR, found with a similar incidence across the board irrespective of the grade of ANH (around 15%).[58] Hence, the aforementioned guidelines and recommendations are not strongly supported by evidence. They are based on the assumption that higher grades of hydronephrosis can be associated with higher grades of VUR, which in turn would place such children at a higher risk for UTI.

The exact indications for a VCUG in patients with isolated hydronephrosis are truly not clear at this stage and probably would be better delineated by a proper randomized trial. Currently, the authors' recommendation is to approach each case individually, taking into account the level of understanding of the family, access to health care and specific imaging findings.

When a decision for a VCUG is made, the test should be performed under antibiotic coverage with a regular urinary catheter or feeding tube, which should be left indwelling whenever urethral obstruction is demonstrated.

Antibiotic Prophylaxis

There is evidence that patients with ANH have a substantially higher risk of pyelonephritis leading to hospitalization than the general population.[65] The incidence of febrile UTI in the ANH group has been reported in the 4%–19% range.[65–67] As summarized in the SFU consensus statement, there is some evidence that the risk increases with the severity of hydronephrosis, presence of drainage impairment and is not necessarily correlated with the presence of VUR.[5] In addition, it seems higher in girls.[65,66] In a study of 206 consecutive patients with ANH, high-grade hydronephrosis carried a 3-fold greater risk of febrile UTI compared to low-grade.[68]

A meta-analysis demonstrated that offering prophylaxis to 8 patients with SFU grades 3 or 4 hydronephrosis would prevent 1 UTI, regardless of their VUR status.[69] However, in analogy to the VCUG discussion, by using a liberal antibiotic prophylaxis policy, one has to acknowledge the large number of patients being exposed to medication (or in the previous case, radiation) unnecessarily. Again, the issue is extremely controversial and alike the indications for VCUG, would probably benefit from a randomized trial. An individualized approach is thus recommended. Evidently, when the conservative pathway is chosen (i.e. no VCUG, no antibiotics), parents should be taught to seek for immediate medical attention during an episode of unexplained fever, when a catheter urine specimen should be obtained and the child placed on antibiotics until the results are available.

Isotope Imaging

In contrast to infection, unilateral obstruction per se rarely poses an urgent threat and thus the information provided by functional imaging does not usually influence early management decisions in infancy. ^{99m}Tc DMSA is best suited for confirming total absence of function in a multicystic dysplastic kidney or for documenting differential function and patterns of parenchymal damage associated with VUR. Dynamic renography with ^{99m}Tc mercaptoacetyltriglycine (MAG3) is used primarily for the diagnosis of obstruction, including furosemide washout as an essential element of the study. Since the information derived from diuretic renography is rarely crucial in the first few weeks or months of life, this investigation can generally be deferred for 4–6 weeks.

Magnetic Resonance Urography (MRU)

MRU is a promising recent addition to the diagnostic armamentarium in patients with prenatal hydronephrosis. Its most appealing advantage is the possibility of providing high-quality anatomical and functional assessment of the urinary tract simultaneously. Some studies have also suggested that MRU would be superior to nuclear imaging studies for the diagnosis of pyelonephritis or renal scarring. An important limiting downside of MRU is the need for general anesthesia in virtually all patients under investigation for antenatal hydronephrosis. In summary, MRU holds promise for the future but is still not widely available and has not been fully incorporated to postnatal investigation protocols.[70]

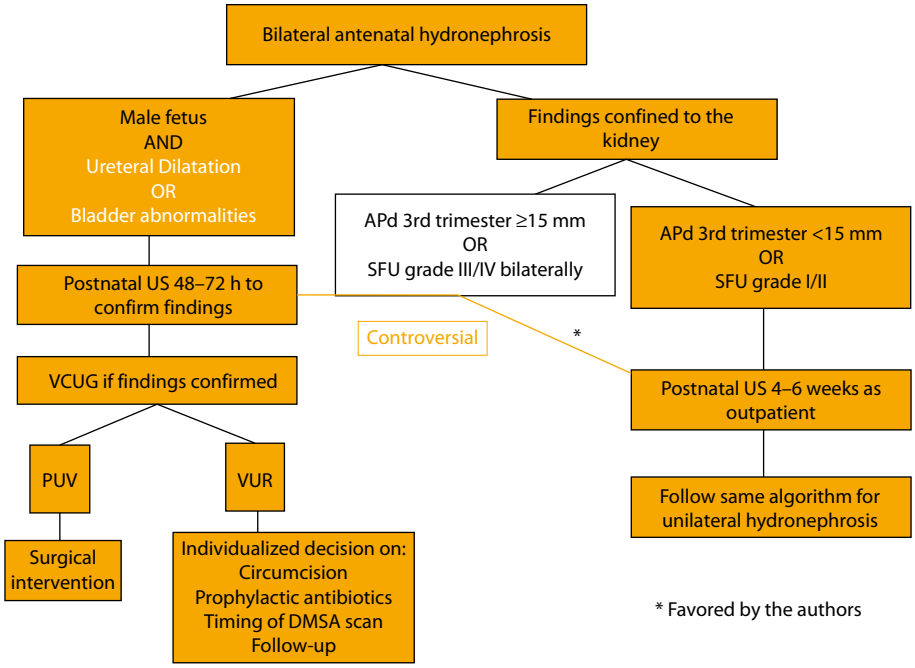
Suggested Protocols for Postnatal Investigation

Postnatal Confirmation and Initial Management of Commonly Prenatally Detected Uropathies

A detailed consideration of the investigation and management of individual urinary tract malformations appears elsewhere in the relevant chapters of this book but some of the key points can be briefly summarized as follows.

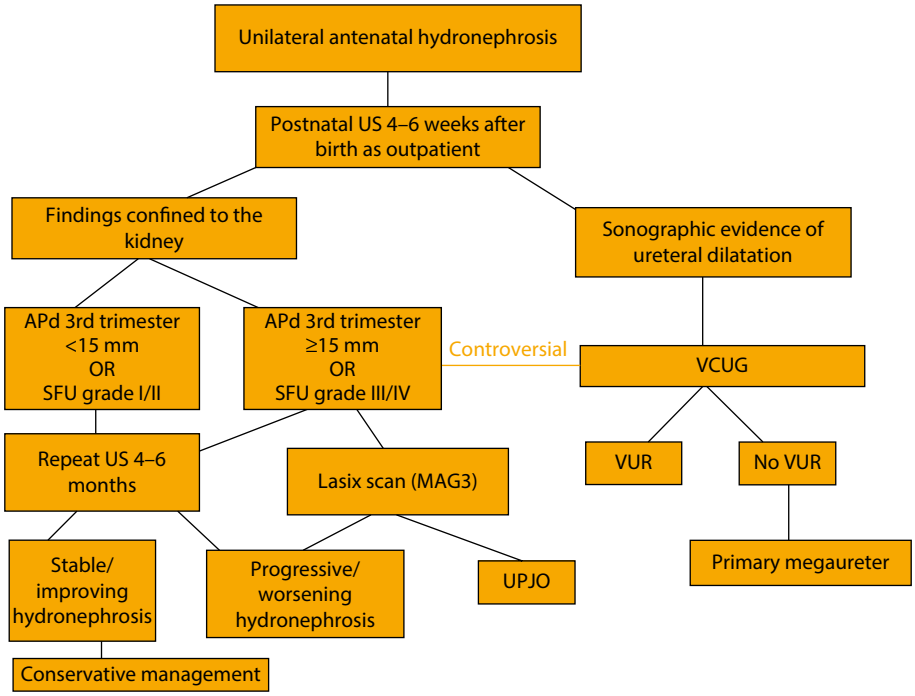
UPJO

UPJO is suspected in the setting of significant isolated dilatation that is confined to the renal pelvis. Establishing an undisputable diagnosis of obstruction is very challenging and the nomenclature is still variable



PROTOCOL 1 Suggested postnatal investigation for prenatally detected bilateral hydronephrosis. Note that highly controversial areas are highlighted with a different color. US, ultrasound; VCUG, voiding cystourethrogram; APd, antero-posterior diameter of the renal pelvis; UPJO, ureteropelvic junction obstruction; PUV, posterior urethral valves; VUR, vesicoureteric reflux.

across centers; some authors will define UPJO based solely on objective parameters such as severe hydronephrosis coupled with significant impairment in drainage and function on the diuretic renogram, thus suggesting a true component of pathologic obstruction. Conversely, others will use the term broadly for any patient with persistent hydronephrosis. The authors prefer to rely on serial ultrasonographys to establish the diagnosis of UPJO since nuclear renogram and even measurement of differential renal function have many pitfalls, i.e.



PROTOCOL 2 Suggested postnatal investigation for prenatally detected unilateral hydronephrosis. Note that performing a VCUG for isolated grades 3 and 4 hydronephrosis is controversial and the authors' preference is NOT to have a VCUG in such a scenario (please see text). US, ultrasound; VCUG, voiding cystourethrogram; APd, antero-posterior diameter of the renal pelvis; UPJO, ureteropelvic junction obstruction; VUR, vesicoureteric reflux.

orientation of the renal pelvis leading to under/overestimation of renal function.[71]

The management of prenatally detected UPJ obstruction has generated considerable controversy and the evolution of a more selective approach to surgery can be largely credited to Ransley's group[72] and Koff.[73] In addition to documenting the potential for the condition to resolve spontaneously, these and other authors have confirmed the relative safety of selective conservative management. Some of the more consistent themes to emerge from the literature are:

1. Significant loss of function which has occurred in utero does not usually recover despite relief of obstruction by pyeloplasty.
2. The probability of significant functional impairment at the time of birth or the subsequent risk of functional deterioration is linked to the severity of dilatation, with the risk of functional impairment being <10% where the AP diameter of the renal pelvis is <20 mm.
3. Conversely, an AP diameter of >35 mm denotes obstruction carrying a significant risk of functional impairment.
4. The risk of functional deterioration on conservative management is low, providing differential function in the obstructed kidney exceeds 40% and the maximum recorded AP diameter of the renal pelvis is <30 mm.

Longpre et al. demonstrated on multivariate analysis that the only predictors of low likelihood of hydronephrosis resolution and need for pyeloplasty (following strict surgical indication criteria) were grade 4 SFU (Figure 3.21) and APD (which averaged 2.9 cm in their surgical group).[74] Based on long-term outcomes data, even for patients with SFU grade 4 hydronephrosis or AP diameter > 2 cm, pyeloplasty will be required in about 50%–55% if strictly objective criteria for surgery are used (i.e. function deterioration <40% or symptoms, such as UTI or stones). Thus, even in this high-risk population, there is room for conservative management.[55]

Posterior Urethral Valves

Currently, antenatal diagnosis in the range of 70%–80% is the most common presentation of PUV in countries where prenatal ultrasonography is performed routinely. However, the true impact of early diagnosis in the natural history is yet to be defined. Results in the literature are conflicting; Ylinen et al. followed 2 groups of patients with PUV (with pre and postnatal diagnosis, respectively) and did not find differences in renal function after 10 years[75] of follow-up. On the other hand, Kousidis et al. observed a higher renal failure rate in boys diagnosed postnatally as well as a higher creatinine in the 2nd decade of life in the same group, suggesting that early diagnosis allows for therapy to be instituted more timely and thus postpone progression of renal dysfunction.[76] Finally, as mentioned earlier, the impact of TOP following prenatal diagnosis on long-term results by excluding the most severe cases should be underscored.

Vesicoureteral Reflux

Primary VUR accounts for 15%–20% of prenatally detected uropathies. In addition, low-grade non-dilating VUR may be identified as an incidental finding on a VCUG performed as part of the routine evaluation of a coexisting prenatally detected uropathy. Prenatally detected VUR is predominantly a disorder of male infant, with males outnumbering females by a ratio of up to 5 to 1.[77] Urodynamic studies in male infants with high–grade VUR have revealed marked bladder dysfunction,[78,79] which has been attributed by some authors to the legacy of transient urethral obstruction in utero—for example, by Cowper's duct cysts.

Regardless of any underlying cause, prenatally detected VUR seems to have a greater potential to resolve spontaneously than clinically presenting reflux. Reviewing the outcome of 413 prenatally detected refluxing units reported in 7 published series, Elder noted an overall figure for spontaneous resolution of 78% for grades I–III VUR and 36% for grades IV and V.[80] Conservative management was effective in the majority, with only 13% of children developing urinary infections during the course of follow-up.

In a study aimed at creating nomograms to predict annual resolution rates of primary VUR, detection on postnatal evaluation for prenatal hydronephrosis was significantly associated with earlier resolution.[81] In another publication, Caione et al. showed that bilateral high-grade VUR diagnosed in the 1st year of life was associated with a risk of chronic renal failure around 50%, regardless of the mode of diagnosis (febrile UTI vs. prenatal abnormality followed by postnatal diagnosis of VUR).[21]

Hence, as outlined in the section on "Postnatal evaluation/VCUG and Antibiotic prophylaxis", the true pathological significance of VUR detected after investigation for prenatal hydronephrosis remains elusive.

Multicystic Dysplastic Kidney (MCDK)

The introduction of prenatal ultrasonography revealed that the true prevalence of MCDK (Figure 3.15) is far higher than was previously recognized.[82,83] The natural history of prenatally detected MDKs is characterized by shrinkage or complete involution—which can also occur in utero, mimicking renal agenesis.[84] Postnatally, the diagnosis of MCDK is usually confirmed with an ultrasonography showing non-communicating cysts without renal parenchyma coupled with a DMSA confirming a solitary functioning kidney on the contralateral side.

Although there are reports of MDK occurring on a familial basis, it more commonly behaves as a sporadic anomaly. In the past, a VCUG was routinely obtained to rule out associated VUR but this approach is no longer recommended. The management of prenatally detected MDKs is considered elsewhere.

Mild Dilatation (pelviectasis)

Mild collecting system dilatation (Figures 3.18 and 3.19), typically a renal pelvic diameter in the range 5–10 mm, is a feature of approximately 1:100 pregnancies. However, this is often a transient phenomenon. For example, Sairam[85] reported an 80% resolution rate for dilatation in the range 4–6 mm. Likewise, Chitty et al[86] followed 475 fetuses with mild dilatation detected between

16 and 26 weeks' gestation, and documented complete resolution or improvement in 66% on re–evaluation in the third trimester. Pelviectasis is sometimes cited as a possible marker for aneuploidy. However, in a study of 25,586 unselected low–risk pregnancies, Havutcu et al[87] documented a 1.25% incidence of mild dilatation (mean AP diameter 6.4 mm, range 5–15 mm) but found no cases of aneuploidy. These authors concluded that the risk (of aneuploidy) in isolated fetal pyelectasis in low–risk populations is so small that it should not be an indication for invasive prenatal karyotyping. Although the weight of reliable evidence indicates that isolated dilatation is not a marker of aneuploidy, when this finding occurs in conjunction with other anomalies it is more strongly indicative of an underlying genetically determined anomaly or syndrome.

In summary, as detailed in the previous sections, low-grade (1 and 2) SFU dilatation confined to the renal pelvis or AP diameter <1.5 cm represent a finding of low significance that maybe does not require additional tests or investigations.[55] Late worsening or recurrent hydronephrosis has been described ranging from 1 to 5%, but the optimal length of sonographic follow-up required (if any) for such patients has not been determined in a proper study.[5]

Megaureter

Unilateral hydroureteronephrosis (Figure 3.22) that is not associated with VUR is likely secondary to primary megaureter. Discussing the classification and management of megaureter is beyond the scope of this chapter but the possibility of obstruction at the ureterovesical junction (UVJ) and consequent renal function deterioration is concerning, similarly to what is seen with UPJO. Therefore, postnatal investigation will usually entail repeated ultrasonographys, a VCUG and a nuclear scan at least to follow the differential function. The accuracy of functional studies with furosemide for obstruction in this scenario is debatable and will be addressed elsewhere. The majority of patients with non-refluxing megaureter will experience spontaneous resolution. Higher grades of hydronephrosis and larger ureteral diameters (above 1cm) are associated with lower resolution rates and higher need for surgery.[88,89]

Duplicated Collecting Systems/Ectopic Ureters/Ureteroceles

The prenatal suspicion of a duplicated collecting system (Figure 3.23) does not mandate any particular action. However, it is important to keep in mind the pathological entities that can present in association with duplication. Hence, the presence of a dilated ureter and segmental dilatation of the (upper) collecting system may denote an ectopic ureter. Alternatively, the presence of a cystic lesion in the bladder (Figure 3.24), which can be associated with ureteral dilatation and upper pole hydronephrosis as well, is suggestive of an ureterocele. The vast majority of patients with antenatally detected ureteroceles are managed postnatally in a non-urgent fashion.

FIGURE 3.23 Segmental hydronephrosis suggesting the presence of a duplicated collecting system.

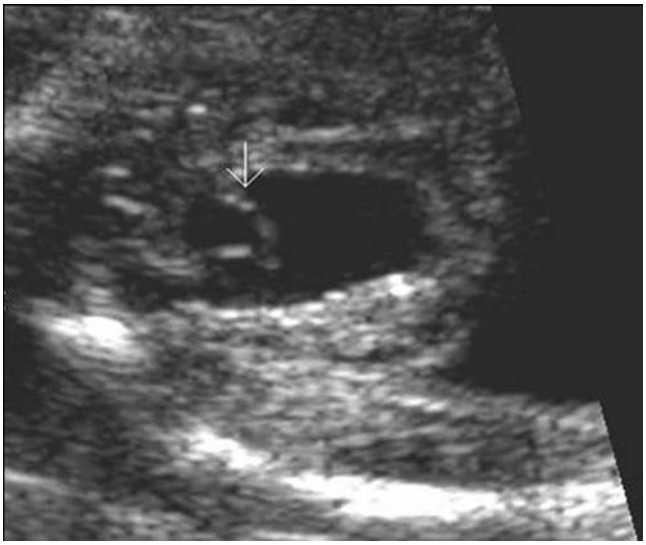


FIGURE 3.24 Finding of cystic lesion within the bladder, which is suggestive of a ureterocele.

Exceptions to that rule are patients with large ectopic ureteroceles causing bladder outlet obstruction (thus mimicking PUV[90]) and prolapsed ureteroceles in females, which may require urgent decompression (Figure 3.25a and b). Although exceedingly rare, prenatal diagnosis of prolapsed ureteroceles with fetal MRI has been described.[91]

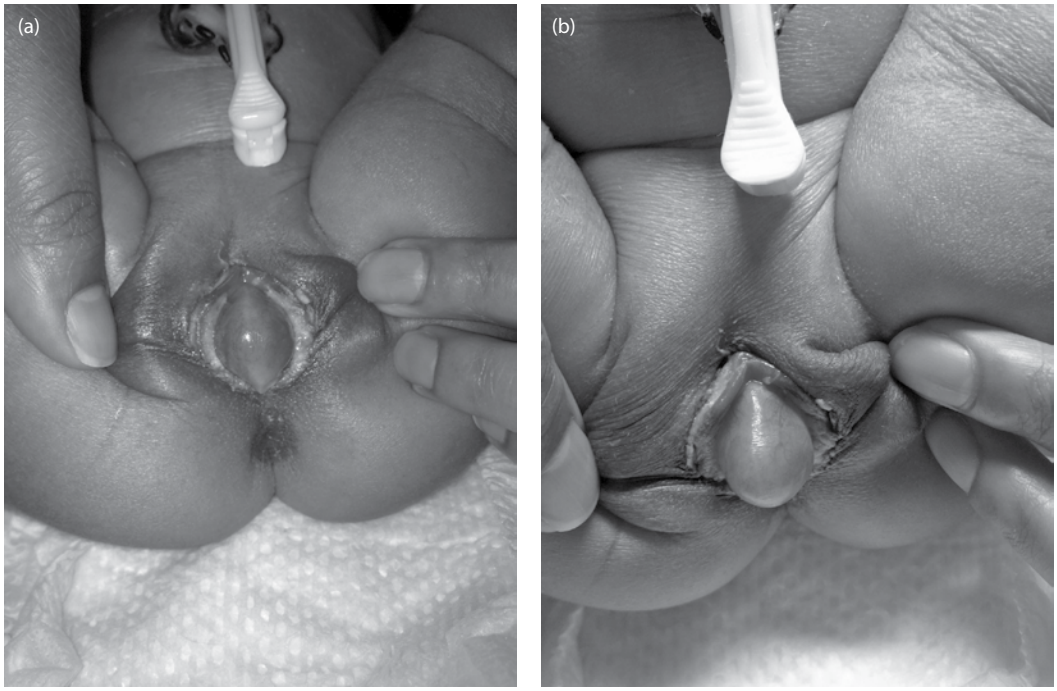


FIGURE 3.25 (a, b) Prolapsed ureterocele in a female neonate; treated with bedside puncture.

CONCLUSIONS

Ultrasonography is now so firmly rooted in obstetric practice that it would be unthinkable for pediatric urology to return to the pre-ultrasonography era. In general, prenatal diagnosis must be considered to have been beneficial, but it must also be acknowledged that the detection of mild dilatation and some asymptomatic anomalies has generated needless parental anxiety and unnecessary investigation. In many countries the impact of termination of pregnancy is already evident in a substantial decline in new cases of prune belly syndrome, cloacal and 'classic' bladder exstrophy and neuropathic bladder associated with open meningomyelocele. As termination of pregnancy extends to include other severe, nonlethal fetal uropathies the number of infants and young children requiring renal replacement therapy and transplantation (predominantly males with urethral obstruction and renal dysplasia) may also diminish.

Prenatal ultrasonography has undoubtedly advanced our understanding of the functional development of the urinary tract and the pathophysiology of many urinary tract malformations. In the future, this will be complemented by important discoveries within the rapidly advancing science of developmental biology to provide pediatric urologists with a much greater understanding of the scientific foundations of the specialty.

Prenatal diagnosis has impacted Pediatric Urology as a specialty uniquely and should encourage the execution of multicentric, prospective, high-quality long-term outcome studies to delineate the exact natural history of many of the problems that are detected, clear indications for prenatal intervention as well as indications for postnatal investigations and treatment.

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CHAPTER

4

In-Office Ultrasonography

Dennis B. Liu and Max Maizels

INTRODUCTION

With technical advancements leading to ever more compact, portable, and less expensive ultrasound units, pediatric urologists have increasingly incorporated ultrasonography into their office practices. Because it gives accurate information quickly, noninvasively, and without x-ray radiation, ultrasound has become a standard, initial diagnostic test to evaluate pediatric urology patients. Previously, we have shown the practicality and benefits of this modality[1–3] and now update this experience. In this chapter, we show how in-office ultrasound (IOUS) advances office practice in the initial evaluation and follow-up of a variety of common pediatric urology office scenarios.

ADVANTAGES OF IOUS IN PEDIATRIC UROLOGY

Referrals to evaluate hydronephrosis, urinary tract infections (UTIs), and enuresis (or dysfunctional elimination) account for approximately 40% of office pediatric urology consultations. Traditionally, initial evaluation begins with a comprehensive office history and physical examination, and referral to a radiologist for a conventional ultrasound exam. IOUS offers several advantages over this traditional approach. As an ultrasound exam may be included in the initial office evaluation, by performing an IOUS, the information derived leads to making working diagnoses and management plans more quickly. It reduces the need to obligate parents for return visits to the urologist after an exam performed off site in a radiology department and allows the opportunity to immediately build physician–patient–family interaction. This opportunity allows better communication with the patient and their families, thus reducing their anxieties and providing them a better understanding of the disease processes. A real-time explanation of the images by the urologist performing the exam to the parents present during the exam solidifies this physician–patient bond. Because the pediatric urologist, as the ultrasound examiner, has the clearest insight into the reason for the exam, this often leads to more exacting diagnoses, as the pediatric urologist will be able to sharply focus the examination performed as an IOUS. For example, bladder dynamics have direct influence on the status of the kidneys. Recognizing this relationship, a pediatric urologist would be able to assess the kidneys with both a full and an empty bladder, often providing more information than images performed by a nonurologist, where examination may not have included this consideration.

PERFORMING IN-OFFICE ULTRASONOGRAPHY

This chapter provides an introduction to perform and utilize ultrasonography for pediatric urology. If you would like a more comprehensive educational experience in IOUS, please visit www.cevlforhealthcare.org.

A wide variety of portable, office-based ultrasound units are available commercially, ranging from large units requiring a wheeled cart to briefcase-sized units and, most recently, handheld devices. In our practice, we use a toaster-sized sector scanner on a wheel cart at our hospital-based office and transport a briefcase-sized unit to satellite offices. We currently perform examinations with either a 5 or 7 MHz probe. For examination of the kidneys of older, larger patients, a low-frequency (3 or 5 MHz) probe is used due to its better tissue penetrance. A higher-frequency probe (7.5 or 10 MHz) is used to image closer objects, such as kidneys and bladders of younger children. Real-time images are displayed on the monitor, and hard copies of the examination may be captured onto flash memory cards or printed directly onto thermal archival paper. Printed images are kept in the patient's charts, allowing the pediatric urologist quick access to the images on subsequent office visits.

A good ultrasound examination requires a calm, cooperative, and still patient. This can be challenging in the pediatric population. The process of preparing the child for the examination begins the moment the child enters the exam room, and thus the room should be warm. The child's clothes can be loosened without disrobing. Adapting a DVD player or tablet computer to the examining platform can be helpful to engage and distract children from the fear engendered from viewing high-tech hospital equipment. Infants can be breast- or bottle-fed, allowing examination of a lulled child. Toddlers frequently fixate on the cartoons playing on the DVD player or tablet. Engaging them in simple word games may distract adolescents. The routine of placing a small terry cloth protective towel over the patient's underwear becomes "like an apron we use to help in the kitchen." Applying ultrasound gel becomes "like sun tan lotion we apply at the pool." Furthermore, warming the gel prior to use with a self-heating unit keeps the child comfortable. Older children

may be offered the opportunity to hold the transducer themselves. Very apprehensive children may be reassured by allowing their parent to apply the ultrasound gel, and the parent can hold the transducer as if he or she is performing the exam with the pediatric urologist manipulating the probe "behind the parent." Other useful tricks can be developed using your own imagination.

For brief instructions on performing an IOUS, please see Video 4.1.

POSITIONING THE PATIENT

Imaging of the Kidneys

We typically begin IOUS by positioning the child supine. Renal imaging in the supine position begins by placing the transducer anteriorly in the right or left subcostal region. The kidneys are imaged through an acoustic window provided by the liver (right kidney) or the spleen (left kidney). If the kidneys are not easily imaged subcostally, intercostal placement of the transducer may help, although pushing here may be uncomfortable and derail the exam. Alternatively, the child may be placed in the lateral decubitus position. In a toddler or youth, this is accomplished by asking the supine child to grab his or her opposite elbow, which causes them to rotate their trunk themselves. If the kidney is "hidden" by an overlying rib, assuming the prone position will provide better images. The prone position also provides a more accurate measure of length, especially when the kidneys are sequestered under a rib. To image the kidney from the prone position, the transducer is placed along the line of a dorsal lumbotomy incision to provide a longitudinal image, or perpendicular to the line to provide a transverse image of the kidneys.[2] In younger and uncooperative children, IOUS may also be performed using a posterior approach, with the caregiver embracing the child. Sometimes, a child fearful of lying supine can be examined effectively while he is standing. Posterior views are obtained.

Imaging of the Bladder and Ureters

Imaging of the bladder is best performed with the child supine. The probe is placed above the pubic symphysis and aimed at the coccyx. Rotating the probe then provides a transverse or sagittal view of the bladder. If dilated, the ureters can be seen "behind" the bladder on transverse views.

To image the ureters longitudinally, the probe is positioned parasagittally, aiming at the opposite half of the pelvis. Thereby, the *right* parasagittal scanning of the bladder displays a sagittal view of a dilated *left* ureter, and vice versa for the *right* ureter. In this view, assessment of the rectum for constipation and the internal genitalia may also be performed.

Common practical experiences of IOUS in office pediatric urology include:

KIDNEY

IOUS is ideally suited to evaluate the kidneys for hydronephrosis, renal length, and duplication anomaly.

Normal Kidney

The normal kidney is readily identified on sonography due to its sharp demarcation from surrounding structures. This sharp demarcation is due to the sonographic interface between the renal capsule and the surrounding perinephric fat. The shape of the kidney is ellipsoid in the longitudinal view (Figure 4.1). Renal length is optimally measured using this view. The normal length of the kidney in the child is dependent on multiple variables, including the side of the kidney and the child's gender, height, weight, race, and age[4,5] (Figure 4.2). In the transverse view, the kidney appears ovular. The renal cortex is typically uniform in appearance and less echogenic than the liver and spleen. In children, the renal medulla (pyramid) is sonographically more prominent than in adults and appears as hypoechoic "pockets" between the renal cortex and the renal sinus, like "seeds in a watermelon." Prominent renal pyramids can occasionally be confused with hydronephrosis, especially in the neonate. This confusion can be avoided by checking if the sonolucencies communicate with the pyelocalyceal architecture (Figure 4.3a). Hypoechoic renal pyramids do not communicate with the renal pelvis, while dilated minor calyces, evident in hydronephrosis, are confluent with the renal pelvis (Figure 4.3b). The hilum is highly echogenic, often referred to as the *central renal complex* (CRC), containing the hilar vessels and fat. To better understand the spatial relationship of ultrasound with the genitourinary system, please view Video 4.2.

Hydronephrosis

IOUS is the workhorse to approach the diagnosis and management of hydronephrosis. Hydronephrosis appears sonographically as sonolucent cavitation of the CRC. Hydronephrosis is graded according to the Society for Fetal Urology (SFU) classification system.[6] This classification system grades hydronephrosis by categorizing the pattern and extent of renal pelvic and calyceal dilation, as

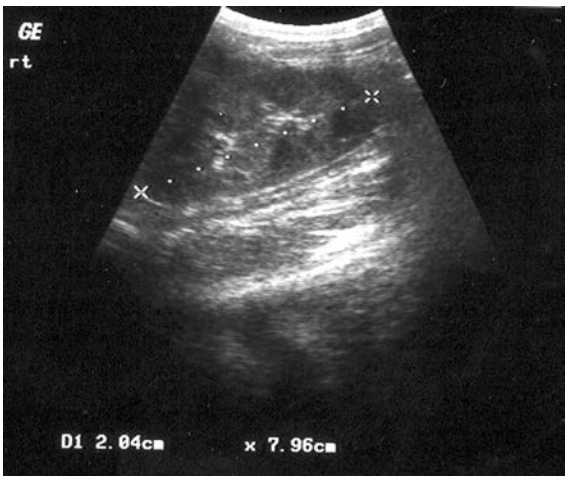


FIGURE 4.1 IOUS. Normal kidney. Longitudinal view of a normal kidney of a 3-year-old boy was done for sibling screening of VUR. The renal length is 80 mm (normal mean, 70 mm ± 10). The CEC is prominent because of its normal echogenicity. There is no hydronephrosis.

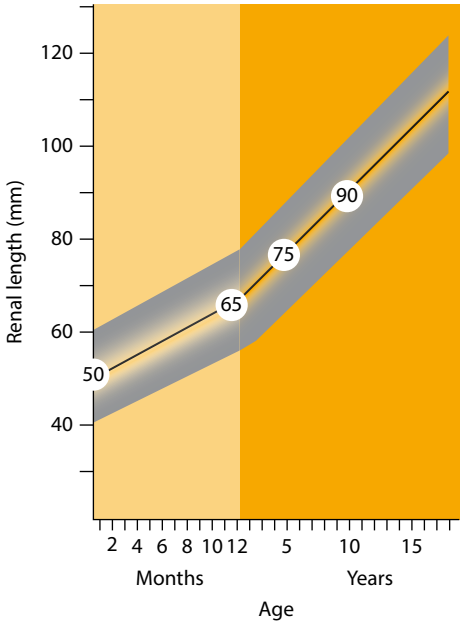


FIGURE 4.2 Nomogram for normal renal size in children. (From Han BK, Babcock DS. *AJR Am J Roentgenol* 1985;145:611–6.)

TABLE 4.1 SFU classification of hydronephrosis

Grade 0	No pelvic dilation. Renal pelvis is empty. Echogenic hilar fat is not split by retained urine.
Grade 1	Minimal pelvic dilation (minimal retention of pelvic urine evident as a thin sonolucent stripe). No calyceal dilation.
Grade 2	Moderate pelvic dilation (broad intrarenal sonolucent stripe, or an extrarenal pelvis). Major calyces may be imaged but are not considered dilated. No minor calyceal dilation.
Grade 3	Large pelvis, dilated major calyces, and minor calyces *uniformly dilated*. Normal parenchymal thickness.
Grade 4	Exaggeration of Grade 3 *with* thin parenchyma.

Source: Fernbach SK et al. *Pediatr Radiol* 1993;23:478–80.

well as renal parenchymal thickness (Table 4.1, Figure 4.4). Hydronephrosis detected on IOUS may be caused by ureteropelvic junction obstruction (UPJO), vesicoureteral reflux (VUR), obstructed upper-pole moiety ureters (ectopic or ureterocele) of a duplex collecting system, high bladder pressure (e.g., neuropathic bladder), or lower urinary tract obstruction (e.g., posterior urethral valves). On the other hand, SFU Grade 2 hydronephrosis may represent a variant of normal as an extrarenal pelvis (Figure 4.4).

As prenatal ultrasound examinations become more common in obstetrical practice, referrals to pediatric urologists to evaluate prenatally detected pyelectasis are becoming more frequent. The degree of prenatal pyelectasis that is clinically significant in predicting postnatal urologic significance has yet to be agreed on. In the postnatal evaluation of prenatally detected hydronephrosis, ultrasound examination is done after newborn discharge, at about 1 week of age. Common postnatal outcomes of prenatally detected hydronephrosis include spontaneous resolution, or the identification of VUR or UPJO. Even if IOUS demonstrates resolution of bilateral prenatally detected hydronephrosis, the child still has a 10%–30% likelihood of occult VUR[7] (Figure 4.5a,b). In this situation, IOUS provides an opportunity for immediate counseling. IOUS also plays an important role in structuring the management and follow-up of prenatally detected hydronephrosis.

Due to its convenience for performing serial exams, IOUS is an ideal modality to follow patients whose parents or family choose observational management for prenatally diagnosed hydronephrosis. In a portion of these patients, hydronephrosis will improve and the child will avoid unnecessary operative intervention (Case 1). When evaluating newborns for hydronephrosis, it is important to delay ultrasound imaging for a few days after birth,

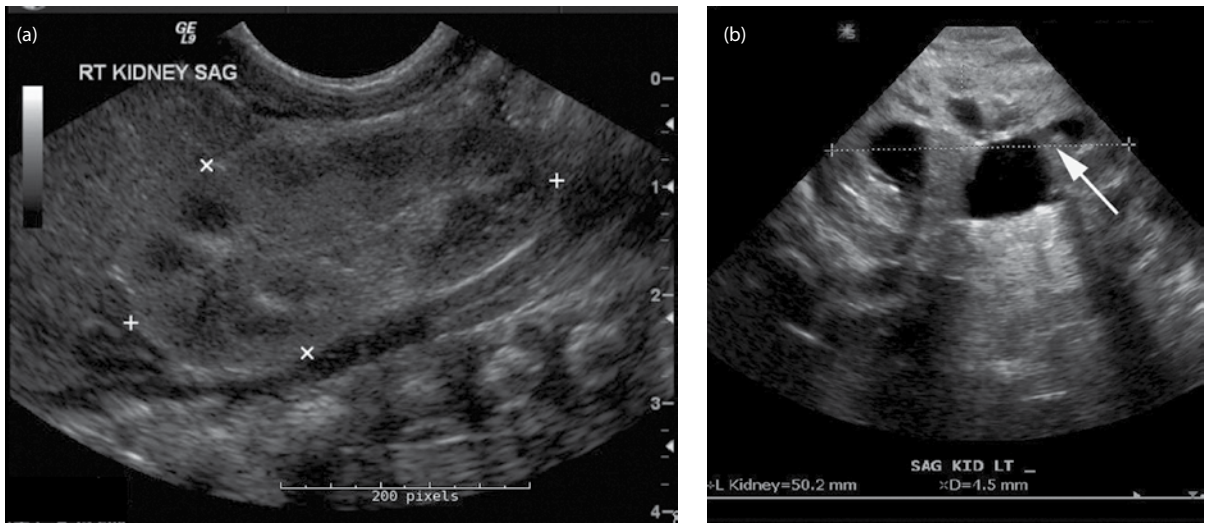


FIGURE 4.3 IOUS. Normal renal pyramids. Longitudinal view of a normal kidney of a 3-month-old girl demonstrates the sonographically prominent renal pyramids in children (a). There is no connection to the renal pelvis. (b) In contrast, there is a connection between the sonolucency and the renal pelvis (arrow).

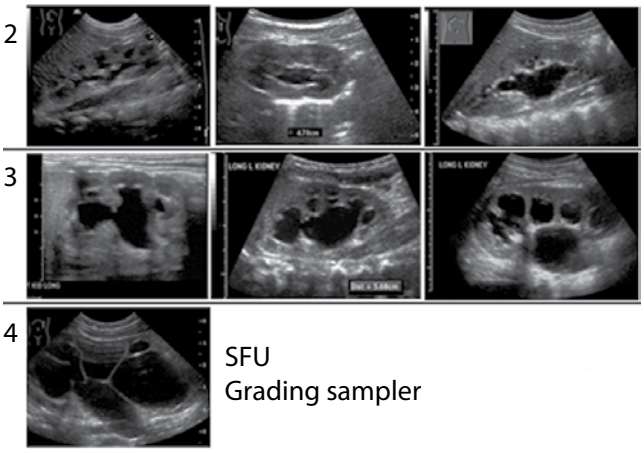


FIGURE 4.4 SFU classification of hydronephrosis. Representative images of kidneys with SFU Grades 2–4. SFU 0 and 1 are intentionally omitted.

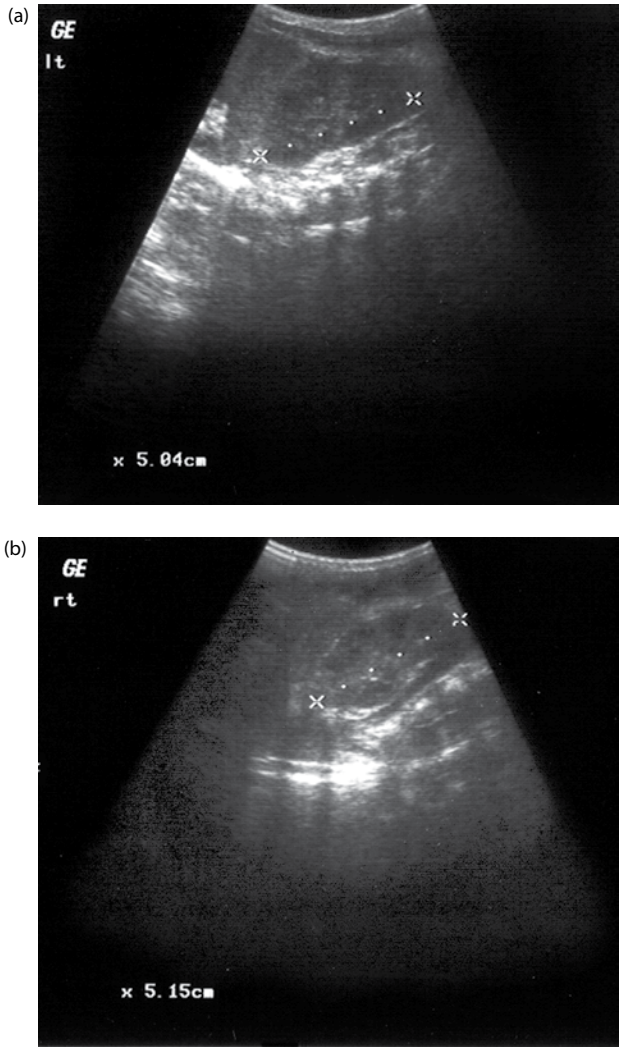


FIGURE 4.5 IOUS is used to follow up prenatally detected hydronephrosis. At 10 days old, the left (a) and right (b) kidneys are normal. These findings correlate with an 80% likelihood of a normal variant and a 20% likelihood of VUR.

as the initial postnatal ultrasound may fail to appreciate hydronephrosis due to the relative dehydration of the neonate.[8,9] Such imaging can be conveniently and expediently done with IOUS once the infant has been well hydrated. Case 2 is a demonstrative illustration of the importance of delayed imaging for Sonographically evident renal pelvis (SERP) by IOUS.

Case 1: IOUS identifies the resolution of fetal hydronephrosis (see Figure 4.6).

Case 2: IOUS is used to follow up premature ultrasonography for fetal hydronephrosis (see Figure 4.7).

In addition to UPJO, hydronephrosis may also be due to VUR. In order to evaluate for VUR, examination of hydronephrosis with both a full and an empty bladder should be performed, as the status of bladder filling directly impacts the appearance of the upper urinary tracts. The following two cases demonstrate the utility of IOUS in providing a more thorough evaluation of hydronephrosis by allowing the examiner to evaluate the upper urinary tracts with both a full and an empty bladder. In both of these cases, the hydronephrosis improved with bladder emptying, and thus dilation is more consistent with VUR than renal obstruction. Because of IOUS, the diagnosis of VUR rather than UPJO was made correctly and without further radiographic testing. By referring patients to radiology for ultrasounds, control of the examination leaves the urologist and often leads to imaging of the kidneys without regard to the status of the bladder fullness. In Case 5, not taking the state of bladder fullness into consideration may have led to an erroneous diagnosis of UPJO.

Case 3: IOUS shows fetal hydronephrosis likely related to VUR (see Figure 4.8).

Case 4: IOUS shows the importance of considering the extent of bladder fullness on hydronephrosis (see Figure 4.9).

Similarly, IOUS provides an important adjunct to evaluate hydronephrosis during the performance of videourodynamics. When performing videourodynamics, the severity of the hydronephrosis can be assessed at varying degrees of bladder fullness and detrusor pressures. This can provide the clinician with important information on the underlying etiology of the hydronephrosis. IOUS performed during videourodynamics is especially important when assessing patients born with posterior urethral valves in whom there is persistence of bilateral hydronephrosis, which may be due to either VUR or elevated bladder pressures.[10,11] Thus, patients with hydronephrosis secondary to elevated bladder pressures would benefit from institution of clean intermittent catheterization to protect their upper tracts.

Case 5: IOUS is an additional dimension to videourodynamic testing (see Figure 4.10).

Anatomic Anomalies

In addition to its role in evaluating hydronephrosis, IOUS is useful to diagnose and structure the management of a variety of anatomic anomalies. Anomalies that can be readily detected by IOUS include duplex collecting

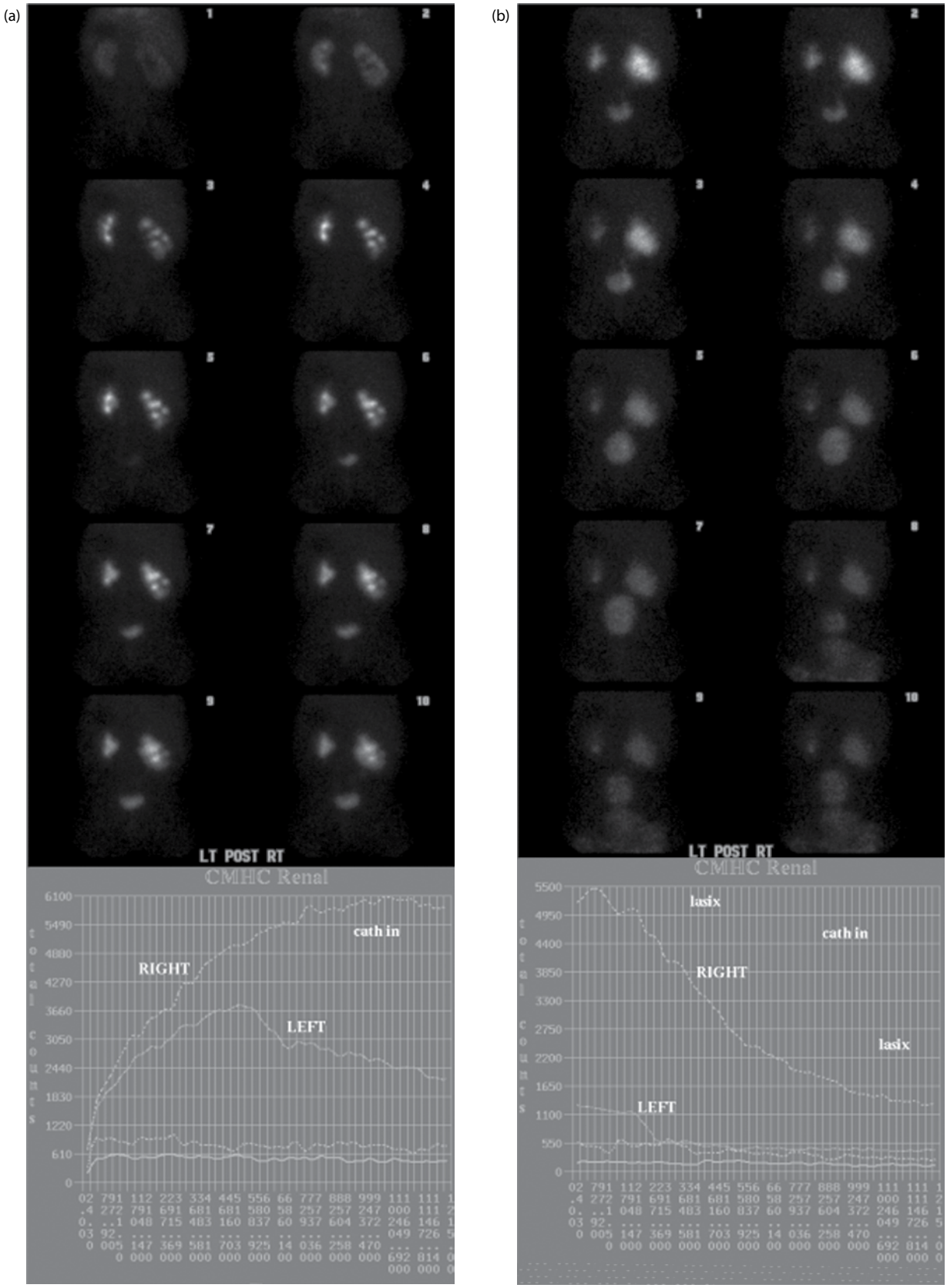


FIGURE 4.6 IOUS identifies the resolution of fetal hydronephrosis. IOUS was done to follow up fetal hydronephrosis. The newborn in-hospital ultrasound shows SFU Grade 4 hydronephrosis (not shown). (a) A diuretic renogram shows the preserved percent differential function in both kidneys with (b) t1/2 drainage = 8.5 minutes. The parents chose observation rather than surgery. (*Continued*)

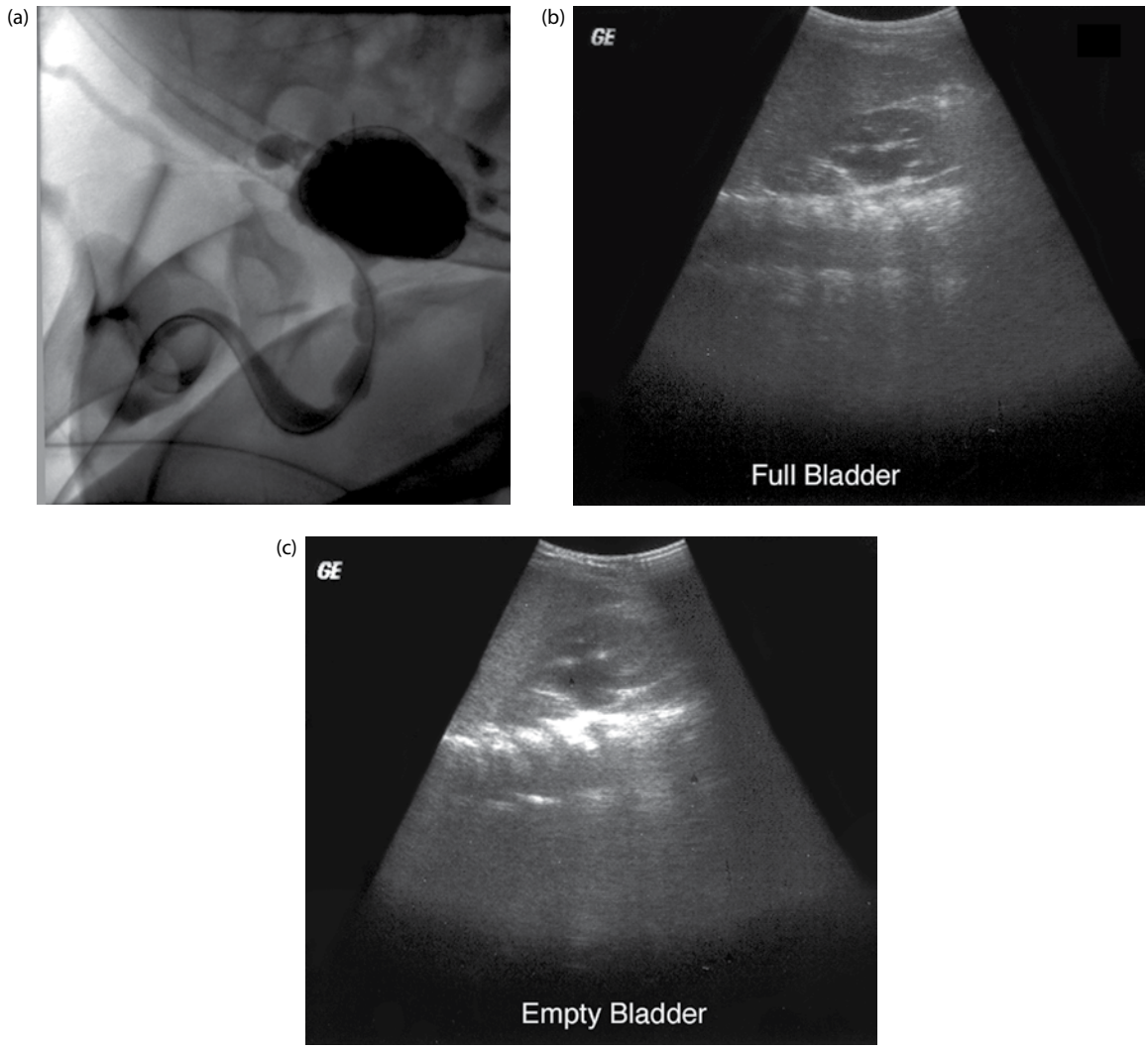


FIGURE 4.10 IOUS is an additional dimension to videourodynamic testing. A 9-month-old boy is status post newborn ablation of posterior urethral valves. Bilateral hydronephrosis persists. (a) The cause for the persistent dilation was not persistent PUV, as the urethra is open on voiding cystourethrogram, or reflux, as the cystogram is normal. IOUS is done simultaneously with videourodynamics to assess if bladder filling increases bladder pressure and so accounts for the renal dilation. IOUS shows stable SFU Grade 3 of the right kidney with the bladder both (b) full and (c) empty. Bladder pressures were less than 40 cm H_2O. The baby has continued to thrive with no further treatment. As the urological testing is normal, it is likely the hydronephrosis will gradually involute over the next 2 years.

Clinical Decision Making in the Management of Vesicoureteral Reflux

The American Urological Association (AUA) guidelines recommend an ultrasound be performed at the initial evaluation of a child with VUR and every 12 months during follow-up. Furthermore, the VUR guidelines deemed ultrasound an option to identify renal scarring in the sibling of a child with VUR, which would then provide rationale for further investigation with cystography.[15] Thus, IOUS, with its inherent advantage of convenience, provides an optimal modality in evaluating and managing patients with VUR.

Postpyeloplasty

In the setting of pyeloplasty, IOUS is used to check for resolution of hydronephrosis, which is typically seen within 2 years postoperatively, and normalization of elongated kidney length, which is typically seen within 5 years postoperatively. Postpyeloplasty imaging with IOUS showing stabilization or improvement of hydronephrosis provides reasonable reassurance of a successful procedure.[16,17] Should IOUS show upgrading of hydronephrosis, especially after the initial ultrasound at 1 month, IOUS is then useful to direct referral for a more complete evaluation with either diuretic renogram or retrograde pyelogram. We perform IOUS to check for a gradual decline in hydronephrosis postpyeloplasty at 1 month, 6 months, 1 year, 2 years, and 5 years postoperatively.

Case 11 (see Figure 4.15).

Postdetrusorrhaphy

Success rates for surgical repair of VUR are approximately 80%–99%.[18] The potential complications of detrusorrhaphy include persistent VUR, new-onset contralateral VUR,

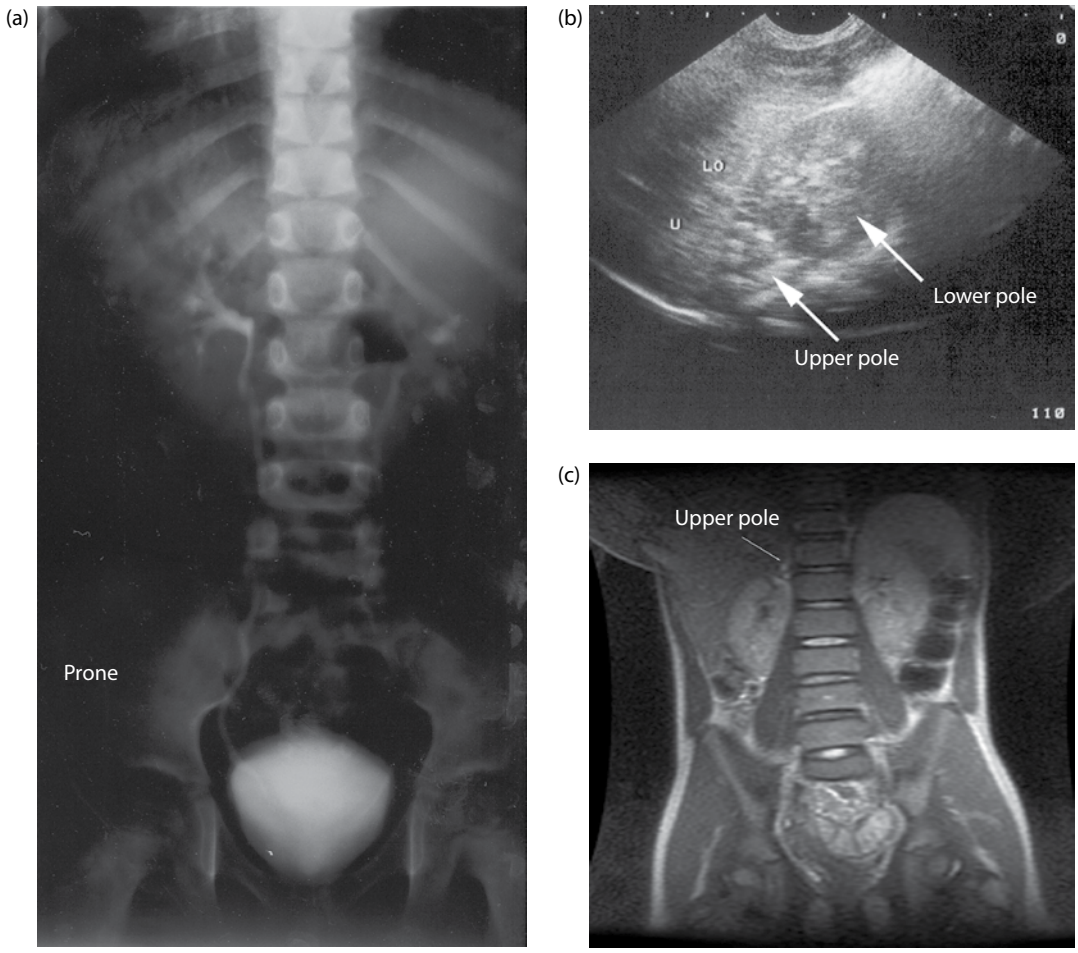


FIGURE 4.11 Duplex collecting system. A 5-year-old girl is evaluated in the office for diurnal enuresis. (a) An IVP (prone view) done previously is interpreted to be normal. Personal review of the hard copies leads to suspicion for an absent *right* upper pole. (b) IOUS is done to answer this concern and shows a bifid pattern that is consistent with renal duplication. (c) The IOUS finding prompted an MRI study, which showed renal duplication and an ectopic ureter. An ipsilateral ureteroureterostomy was performed and the enuresis resolved. This case exemplifies the use of IOUS to evaluate common outpatient pediatric urologic complaints, including enuresis. By performing an IOUS at the time of the visit, the suspicion of a duplex collecting system was pursued and led quickly to a more conclusive radiographic study (MRI), which diagnosed an ectopic ureter.

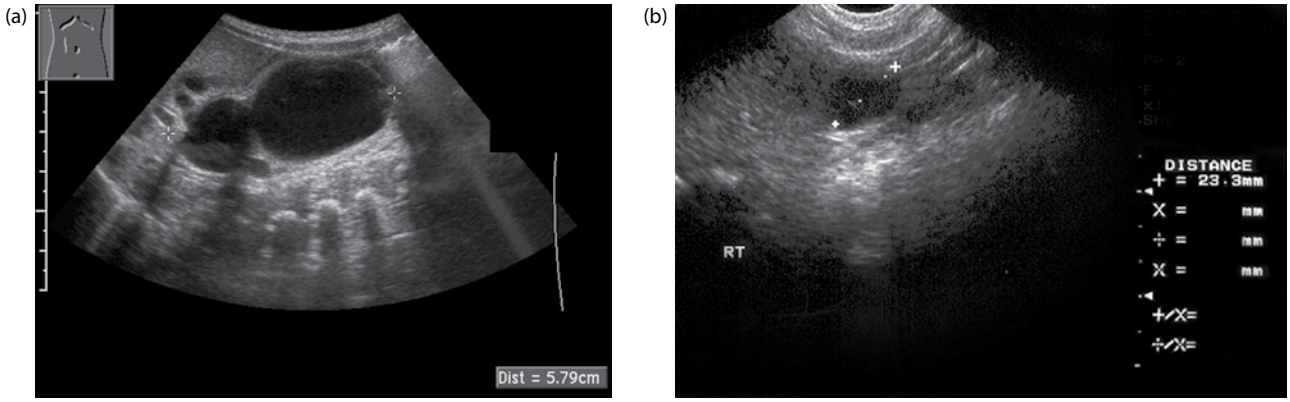


FIGURE 4.12 IOUS shows involution of an MCDK. Fetal ultrasounds of the right kidney have shown an MCDK. (a) The newborn ultrasound confirms this finding. (b) IOUS is performed 1 year later for follow-up. There is involution of the right kidney, thereby confirming the diagnosis of an MCDK.

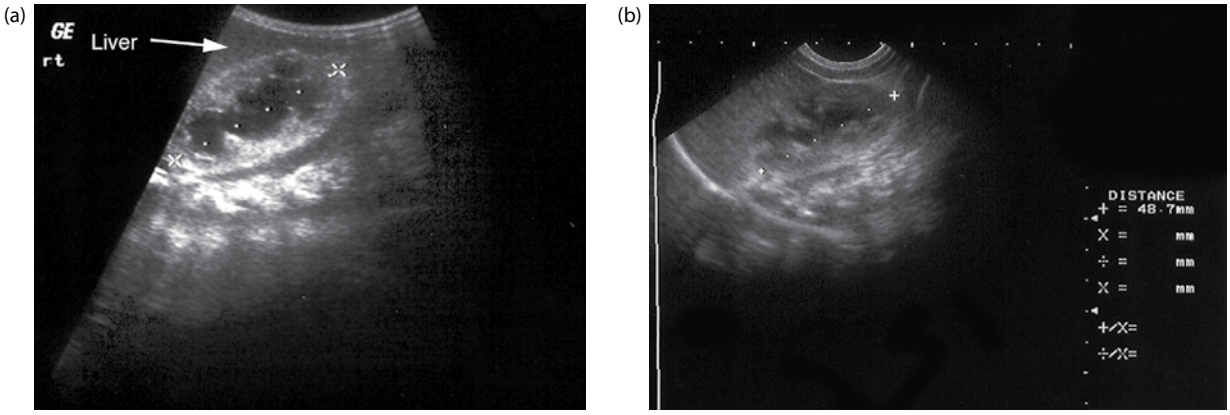


FIGURE 4.13 IOUS to follow up an echogenic, hydronephrotic kidney. (a) This neonatal boy has a renal parenchyma that is more echogenic than the liver. There is SFU Grade 3 hydronephrosis. The contralateral kidney is an MCDK (not shown). Furthermore, his older sister showed bilateral UPJO with renal hypoplasia. (b) IOUS at 3 months' follow-up shows the right kidney is echoechoic with the liver and there is less hydronephrosis (SFU Grade 2 hydronephrosis). Further management includes continuation of IOUS to survey hydronephrosis.

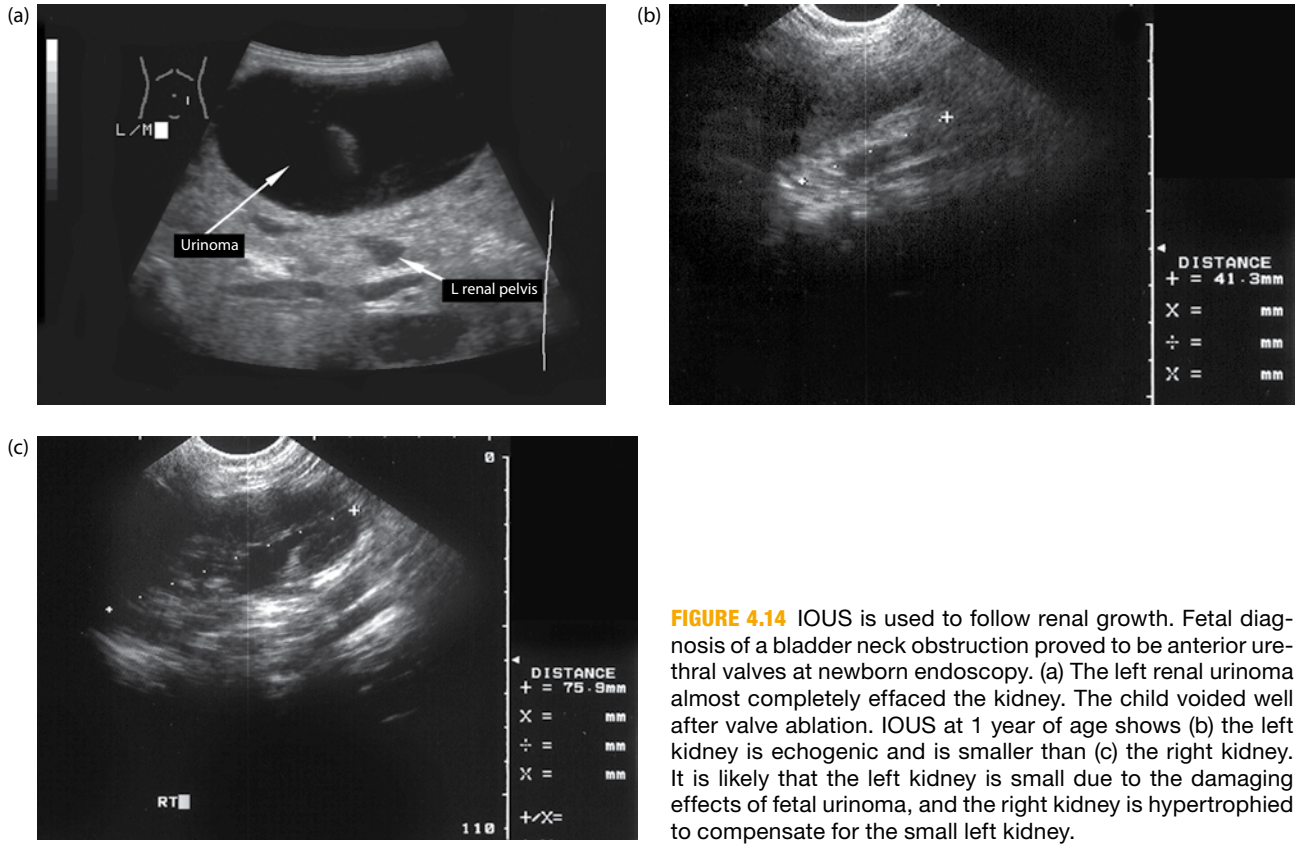


FIGURE 4.14 IOUS is used to follow renal growth. Fetal diagnosis of a bladder neck obstruction proved to be anterior urethral valves at newborn endoscopy. (a) The left renal urinoma almost completely effaced the kidney. The child voided well after valve ablation. IOUS at 1 year of age shows (b) the left kidney is echogenic and is smaller than (c) the right kidney. It is likely that the left kidney is small due to the damaging effects of fetal urinoma, and the right kidney is hypertrophied to compensate for the small left kidney.

and obstruction at the UV junction, any one of which might be detected as new or worse hydronephrosis on IOUS.

Case 12 (see Figure 4.16).

URETERS

In addition to visualizing the kidneys, IOUS may be used to image the ureters. Normal ureters are not dilated and thus are not imaged. However, dilated ureters are readily identified. Ureteral dilation is also graded according to the SFU classification system (Table 4.2).[4] Dilated ureters may accompany hydronephrosis. When ureteral dilation is present without hydronephrosis, the differential diagnosis includes VUR and primary megaureter (nonobstructive and nonrefluxing). When ureteral dilation is present with hydronephrosis, the diagnosis of a ureterovesical junction (UVJ) obstruction should be considered. By combining the SFU scores of hydronephrosis (HN) with hydroureter (HU), a SFU HUN score is calculated (SFU HN + SFU HU = SFU HUN score). We use the SFU

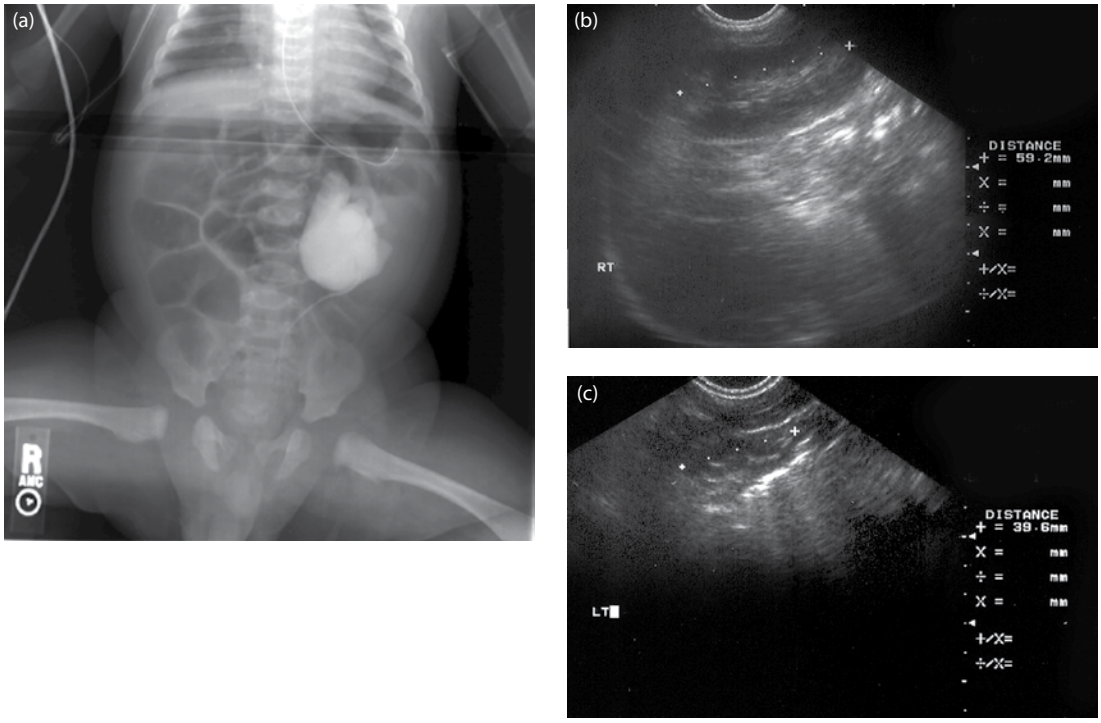


FIGURE 4.15 (a) Pyeloplasty was done for UPJO. (b) By 1 year postop, the IOUS reveals a normal right kidney and only SFU Grade 2 hydronephrosis on the left (c).

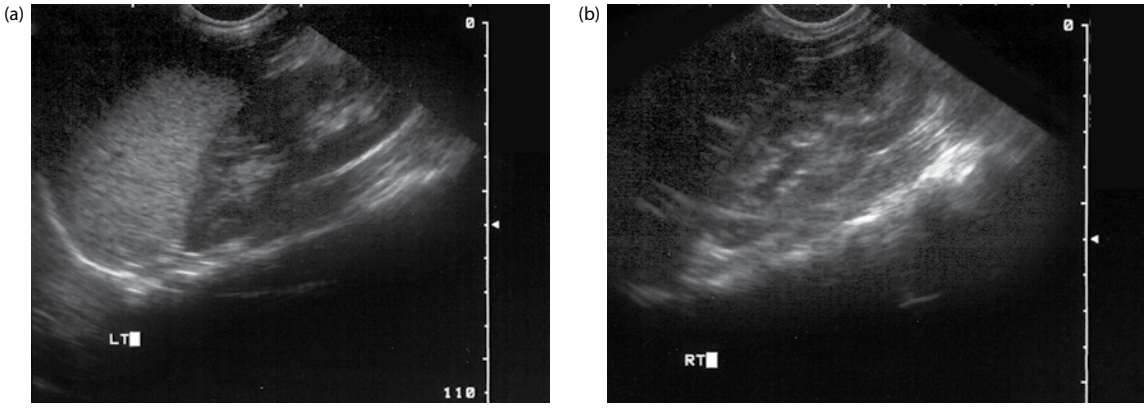


FIGURE 4.16 A 6-year-old girl with breakthrough febrile UTIs and VUR underwent bilateral detrusorrhaphy. (a and b) Two weeks postoperatively, IOUS shows normal kidneys without hydronephrosis and the bladder is empty postvoid (not shown).

TABLE 4.2 Grading of ureteral dilation

Grade 1	Less than 7 mm
Grade 2	7–10 mm
Grade 3	Greater than 10 mm

Source: Chen JJ et al. *J Urol* 2002;168:2149.

HUN score to help predict the presence or absence of obstruction, with a score of 5 or greater predictive of obstruction.[4]

Case 13: Nonobstructive, nonrefluxing primary megaureter (see Figure 4.17).

BLADDER

IOUS can be used to assess megacystis and completeness of bladder emptying, and for follow-up after endoscopic ureterocele incision.

Normal Bladder

The normal bladder, which is best assessed when partially filled or full, is smooth- walled and symmetrical and filled with echolucent urine without any other internal echoes. Urine within a neonate's bladder, however, may be echogenic, which has been attributed to the elevated levels of the Tamm–Horsfall protein. The normal capacity of the bladder may be estimated based on the age of the patient

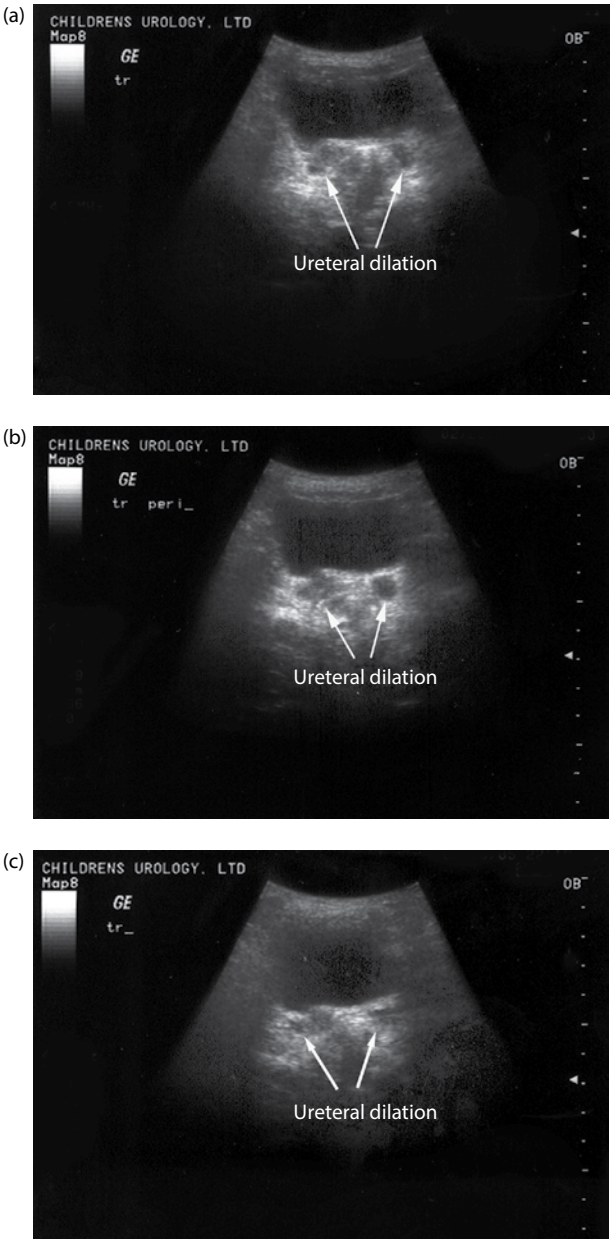


FIGURE 4.17 At 1-year follow-up for fetal SERP, IOUS shows SFU Grade 2 hydronephrosis of the kidneys (not shown). (a–c) IOUS shows that the ureter diameter fluctuates over a 30-second interval without change in bladder appearance. This represents ureteral peristalsis. These findings are consistent with nonobstructed, nonrefluxing megaureters. IOUS continues a longitudinal follow-up.

by the formula Bladder volume (oz.) = Age (years) + 2.[19] Sonographic measurement of bladder volume is obtained by measuring the transverse, longitudinal, and anteroposterior dimensions and employing the formula Bladder volume (mL) = Length (cm) × Width (cm) × Height (cm) × 0.52. IOUS may be used to measure the detrusor thickness while evaluating children with voiding dysfunction. Although the thickness of the detrusor appears distinct in the sonographic examination of the bladder, the normal thickness of the bladder wall is dependent on the extent of bladder fullness. Normative values have been described; however, no consensus has been reached.[20–23] IOUS, though, continues to be useful in following the course of bladder treatments.

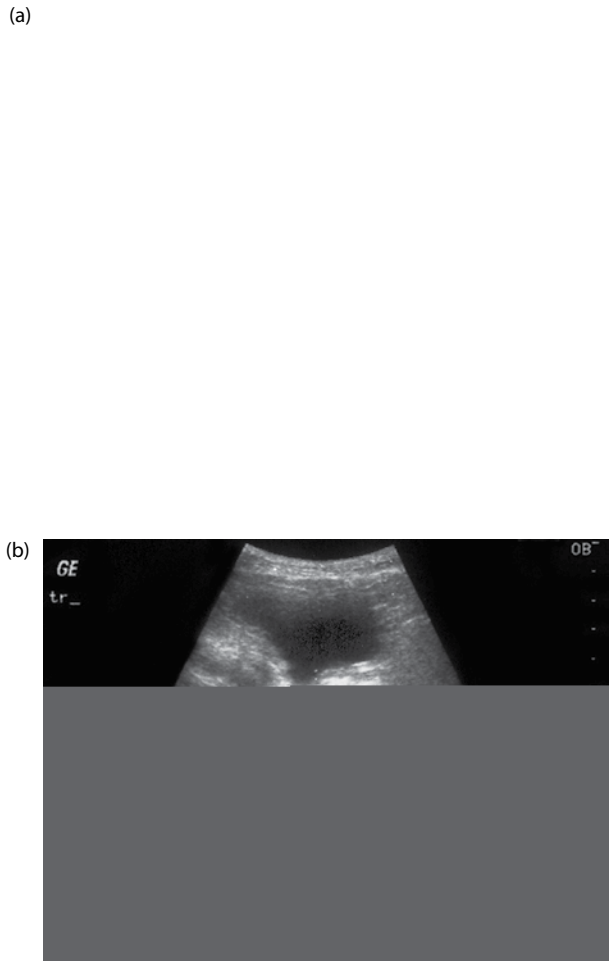


FIGURE 4.18 IOUS diagnoses megacystis or thickened detrusor. This newborn experienced a cerebral hemorrhage and acquired a neurogenic bladder. The voiding cystourethrogram showed an enlarged bladder and bilateral VUR. Intermittent bladder catheterization was instituted along with medical therapy for the cerebral hemorrhage. Oral urecholine was begun as catheterization was tapered. (a) After hospital discharge, IOUS shows a thickened detrusor. (b) After 6 months, the detrusor thickness resolved, and the diaper pattern confirmed good bladder emptying. In this case, the combination treatment with Clean Intermittent Catheterization (CIC) to ensure bladder emptying and oral urecholine to encourage bladder contraction was empiric.

Case 14: IOUS diagnoses megacystis or thickened detrussor (see Figure 4.18).

Ureterocele

Ureteroceles are commonly detected during the evaluation of hydronephrosis. The diagnosis may be missed when other causes of hydronephrosis, such as reflux, are also present. Careful evaluation of the bladder with ultrasound remains the best imaging modality to diagnose ureteroceles. Patience during the IOUS to permit the bladder to empty as the infant voids allows imaging during various stages of bladder fullness. This is important, as varying

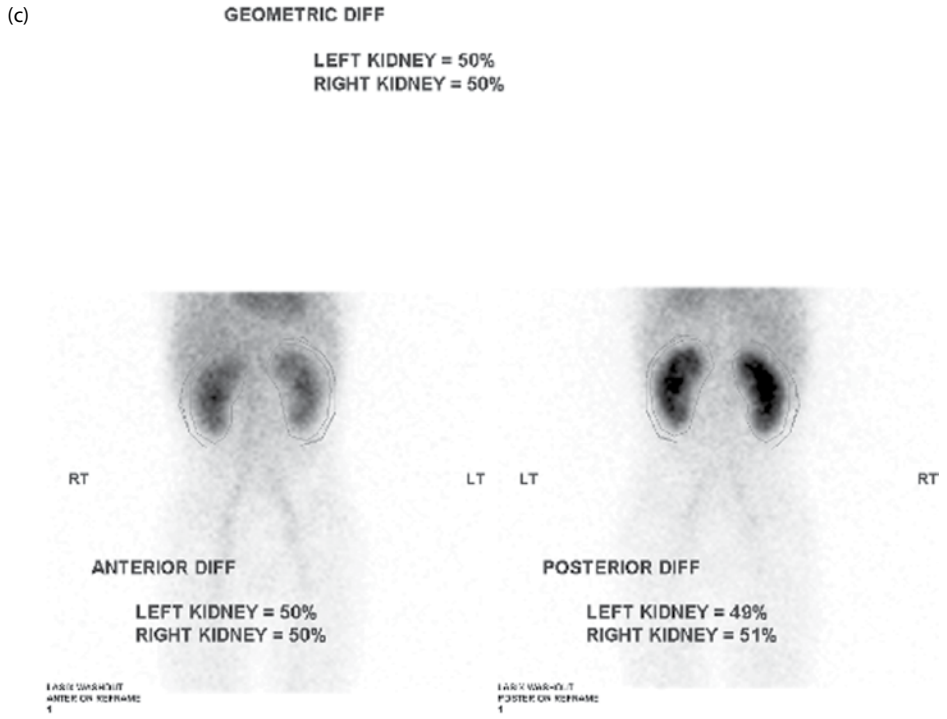


FIGURE 5.1 (Continued) (c) The geometric mean differential function was 50% in the left kidney and 50% in the right kidney.

and excludes the renal parenchyma. If hydroureter accompanies hydronephrosis, the ROI should include the ureter as well. An ROI for background subtraction is drawn lateral and inferior to the lower pole of the dilated collecting system. The drainage of the radiotracer from the pelvicalyceal system is calculated automatically and expressed as T 1/2. By increasing urinary flow after a diuretic, the dilated system may clear in the nonobstructive system. However, in the case of a mechanical obstruction, the narrowed area in the drainage route may prevent the drainage and the time–activity curve may show minimal or no evidence of downsloping. Several important points have to be made regarding assessing diuretic washout curves. First, the T 1/2 is invalid when performed on normal kidneys that have already emptied their pelves. Second, when there is poor renal function, the kidneys cannot be evaluated, as there may be poor, if any, response to the furosemide stimulation. Finally, in large hydronephrotic kidneys (pelvic volume greater than 75 mL), there will be a significant delay in emptying due to a dilution effect even though there may be no mechanical obstruction. In general, prolongation of the T 1/2 correlates with obstruction at the extremes of values. For instance, T 1/2 values of <10 minutes are accurate to exclude obstruction. Alternatively, the lack of any drainage of radiotracer (i.e., T 1/2 "infinitely long") confirms high-grade obstruction. In between, the T 1/2 becomes relatively equivocal, necessitating other clinical parameters and/or repeat assessment by diuresis renography in order to make the diagnosis of obstruction. In neonatal hydronephrosis, the natural behavior of hydronephrosis is variable and may change over time.[11] If there is no evidence of a high-grade obstruction, in uncomplicated cases, a close follow-up may be the best approach.[19]

Radionuclide Cystography

A large number of children are seen because of urinary tract infection (UTI) and vesicoureteric reflux, and radionuclide cystography (RNC) is the preferred method of follow-up because of the low radiation dose compared with conventional radiographic techniques.[19]

In direct radionuclide cystography (DRC), ^{99m}Tc-pertechnetate or sulfur colloid is instilled into the bladder via a catheter in conjunction with a saline infusion.[20] In contrast to radiographic voiding cystourethrography (VCUG), continuous recordings can be done during the bladder filling and voiding phases with no extra patient radiation (filling, voiding, and postvoiding phases) (Figure 5.2). Thus, chances of documenting reflux are enhanced. After the child voids, the residual counts can be used to quantify reflux and voiding volumes, since the concentration of isotope in the solution used to fill the bladder is known.

Indirect radionuclide cystography (IRC) following a ^{99m}Tc-DTPA or MAG3 renal scan is an alternative method to detect vesicoureteric reflux. It should be carried out once the radioisotope has completely cleared from the upper tract and accumulated in the bladder. The child is then asked to void while reflux is assessed (Figure 5.3). This method is more physiological due to the absence of bladder overfilling and has the advantages of additional information about the renal function without the need for catheterization.[21] However, the patient should be cooperative and toilet trained (>3 years old), and the radiation higher than DRC. Although this method compares favorably with micturating cystography and cystoscopy in some hands, overall, the sensitivity to detect the reflux is much lower than that of DRC.

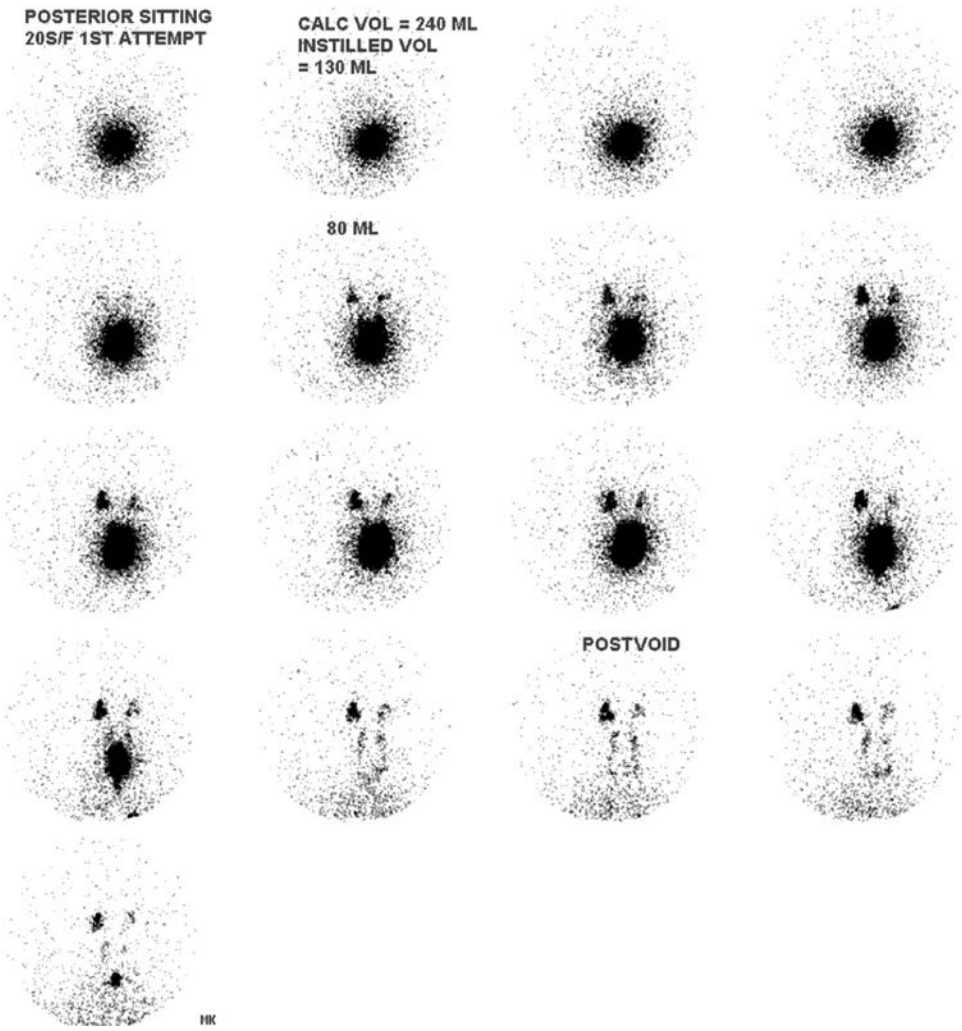


FIGURE 5.2 DRC showed that bilateral vesicoureteral reflux started at 80 mL volume during the filling phase and continued during the voiding images.

Because RNC does not provide the same anatomic detail as VCUG for the evaluation of anatomical structures, such as the PUV in a boy, a VCUG is required. The grading system of RNC and VCUG is different. With RNC, a grade 1 reflux is the visualization of the activity in the ureter (equal to grade 1 in VCUG), a grade 2 is the activity reaching the collecting system (equal to grades 2 and 3 in VCUG), and grade 3 is a dilatation of the collecting system and ureter (equal to grades 4 and 5 in VCUG).

The amount of radiation is lower in DRC than in VCUG (1 mrad/min in DRC; at least 75 mrad in VCUG, depending on the number of films taken and the fluoroscopy time). The use of modern grid-controlled variable-rate pulsed fluoroscopy has reduced the gonadal effective radiation dose by 8-fold; however, it is still 10-fold higher than for RNC.[22,23] Moreover, intermittent reflux may be missed if continuous monitoring is not performed during the filling and voiding phases. Continuous monitoring with fluoroscopy is not acceptable because of increased radiation, while in DRC the radiation will not change. RNC is appropriate for follow-up evaluation of reflux, for screening asymptomatic siblings of a patient with reflux, and for the initial evaluation of girls unless an anatomic abnormality, such as ectopic ureter or ureterocele, is suspected. For the initial evaluation of boys, it is suggested to perform a VCUG in the first assessment to exclude an anatomical abnormality in the urethra and bladder.[23]

Renal Cortical Imaging

The radiotracer of choice for the evaluation of the renal cortex is ^{99m}Tc-DMSA. Images are obtained 2–3 hours after the administration of the radiotracer when the background activity is minimal. Mild decreased activity over the area of the pelvicalyceal system is a normal finding; however, the presence of hydronephrosis correlates with increasing photopenia. Flattening of the upper lateral region of the left kidney due to splenic impression (Figure 5.4) or indentations in the contour of the kidney due to fetal lobulation are normal. External attenuation may also mimic a cortical defect. A ^{99m}Tc-DMSA renal scan is useful to evaluate ectopic kidney and horseshoe kidney; to assess the functioning cortical tissue in a dysplastic or small kidney, the DRF, and differentiation of hypertrophic columns of Bertin versus a tumor, in acute pyelonephritis; and to detect renal scars.

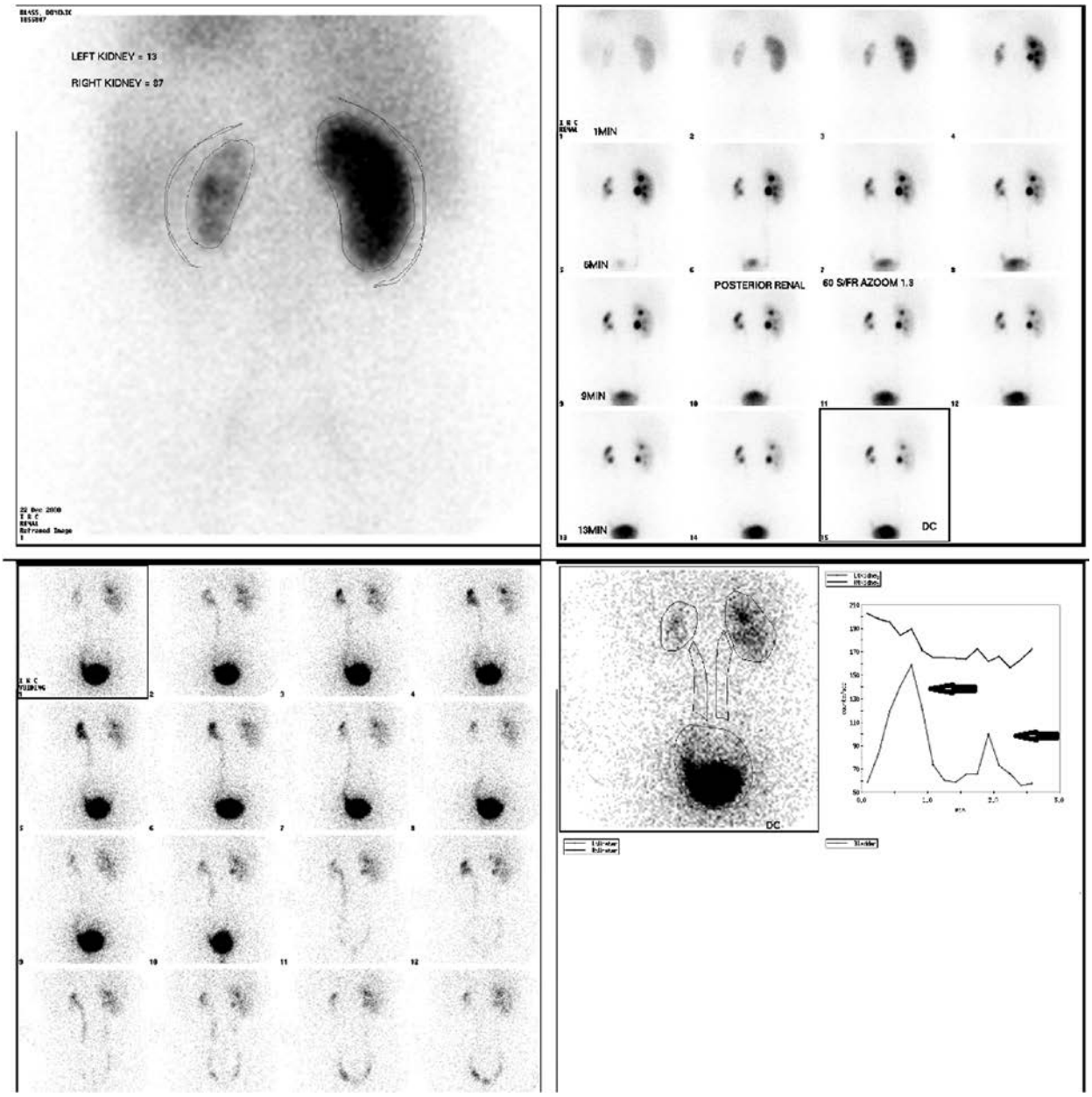


FIGURE 5.3 IRC in a 7-year-old boy shows reflux into the left kidney during the voiding phase. The study also provides further information about the function of the kidneys. The right kidney shows good uptake of the agent, followed by prompt excretion and normal drainage. The left kidney is smaller than the right kidney, with decreased differential function. The posterior differential function is 13% in the left kidney and 87% in the right kidney.

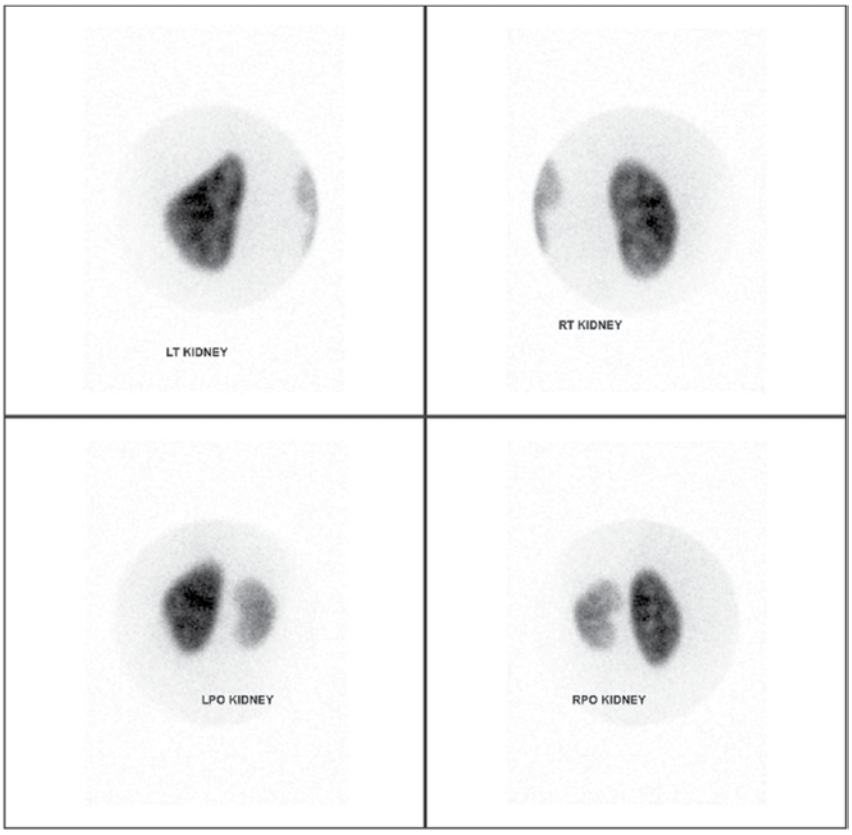
Acute Pyelonephritis

In children with UTI, radionuclide techniques are frequently performed. Direct radionuclide cystogram is the most sensitive method to detect reflux, which is present in approximately a third of children with febrile UTI. DMSA scintigraphy may be helpful in evaluating a child with febrile UTI to determine whether acute pyelonephritis is present—or has occurred.[24] Recently, some investigators suggested a so-called top-down approach with a DMSA scan as the first-line study instead of an RNC because of the relative importance of renal damage rather than reflux in these patients.[25,26]

Acute pyelonephritis appears as a single or multifocal area of decreased accumulation of ^{99m}Tc-DMSA without volume loss (Figure 5.5). Sometimes it may be revealed as a diffuse decrease in radiotracer activity. Although SPECT is better in defining the location of the lesions, it has only a marginal increase in sensitivity and a lower specificity.[27] However, it is useful for the detection of size and multiplicity of the lesions.[28]

A major concern after an episode of acute pyelonephritis is the development of scars (Figure 5.6). Ultrasound is not sensitive enough to detect renal parenchymal scars. Temiz et al. showed that, irrespective of the reflux grade,

(a)



(b)

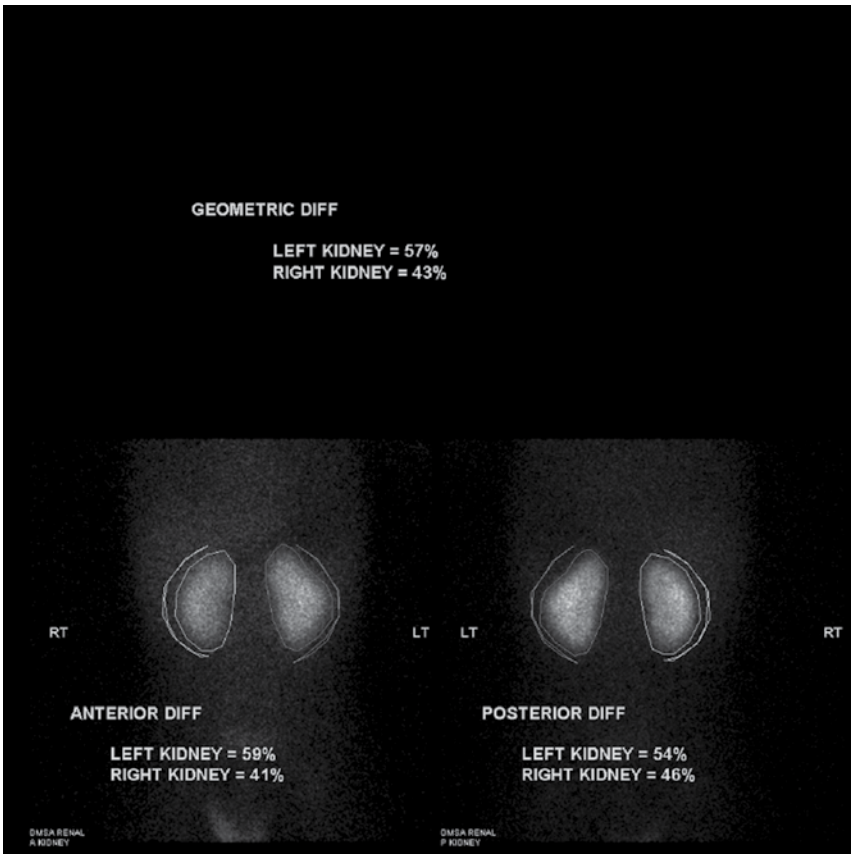


FIGURE 5.4 (a) Normal DMSA scan. Both kidneys show good uptake of the agent without any focal cortical defect or loss of volume. Note the splenic impression over the upper lateral border of the left kidney. (b) The geometric mean differential function is 57% in the left kidney and 43% in the right kidney.

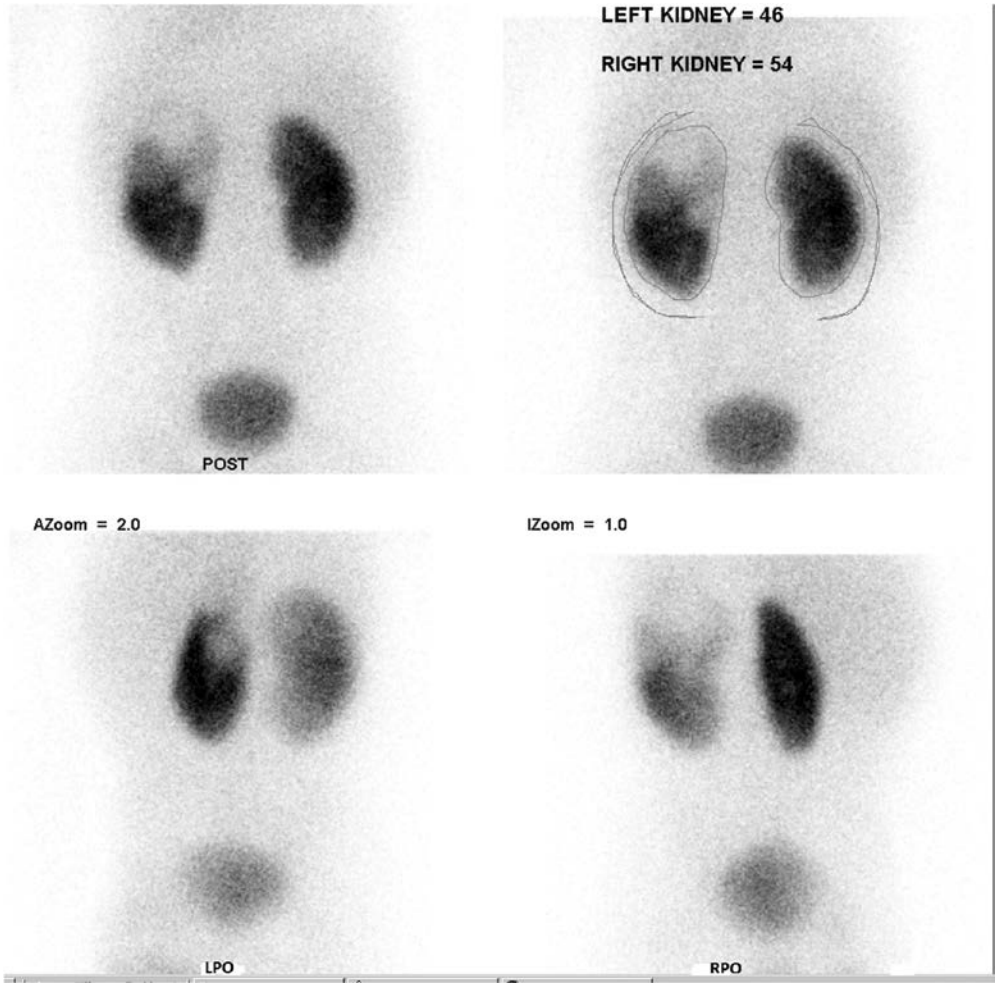


FIGURE 5.5 DMSA renal scan in a patient with febrile UTI shows decreased uptake in the upper half of the left kidney, which suggests acute pyelonephritis.

^{99m}Tc-DMSA scan detected scars in 35% of the kidneys reported to be normal on ultrasound.[29] Others have found similar low sensitivity for ultrasound to detect renal scars.[30,31]

The possibility of renal damage is increased when the patient has a high fever and septicemia in acute pyelonephritis, in atypical forms of microorganisms, when the patient fails to respond to antibiotic therapy after 48 hours, in different treatment regimens, and in repeated infections.[32,33] Decreased cortical uptake after an acute pyelonephritis may resolve during several months or may lead to a permanent scar formation. A follow-up ^{99m}Tc-DMSA study at least 6 months after the acute pyelonephritis may be useful to detect scarring.[34] With ^{99m}Tc-DMSA SPECT, not only is it easier to define whether scars are present, but also location and definition are enhanced.[28]

CONGENITAL ANOMALIES

Ectopic kidneys: Ectopic kidneys (Figure 5.7) are seen well with the nuclear scan, despite bowel gas or bony structures that sometimes obscure the ectopic kidney to intravenous pyelogram (IVP) and ultrasound. The diagnostic dilemma of a solitary kidney on IVP can be sorted out with the aid of a renal scan and ultrasound. These latter two modalities will distinguish renal ectopia from hypoplasia or agenesis.

Horseshoe kidney: The horseshoe kidney (Figure 5.8) poses a special problem. It is often difficult to decide on the IVP if there is functioning renal tissue joining the lower poles of the kidneys because this part of the kidney overlies the spine. If one employs DMSA and takes anterior images, it is possible to detect the presence or absence of functioning tissue in the isthmus; Wilms' tumor, with which a horseshoe kidney is sometimes associated, can occasionally be identified. If horseshoe kidneys are slow to drain, one can assess obstruction using a diuretic renal scan (Figure 5.9).

Duplex kidney: The radionuclide renal study is frequently used to confirm the presence of *renal duplication*, suspected on IVP or ultrasound, or may even diagnose unsuspected cases. The function of each moiety can be individually assessed as well. The upper and lower parts of the duplex kidney are quantified relative to each other,

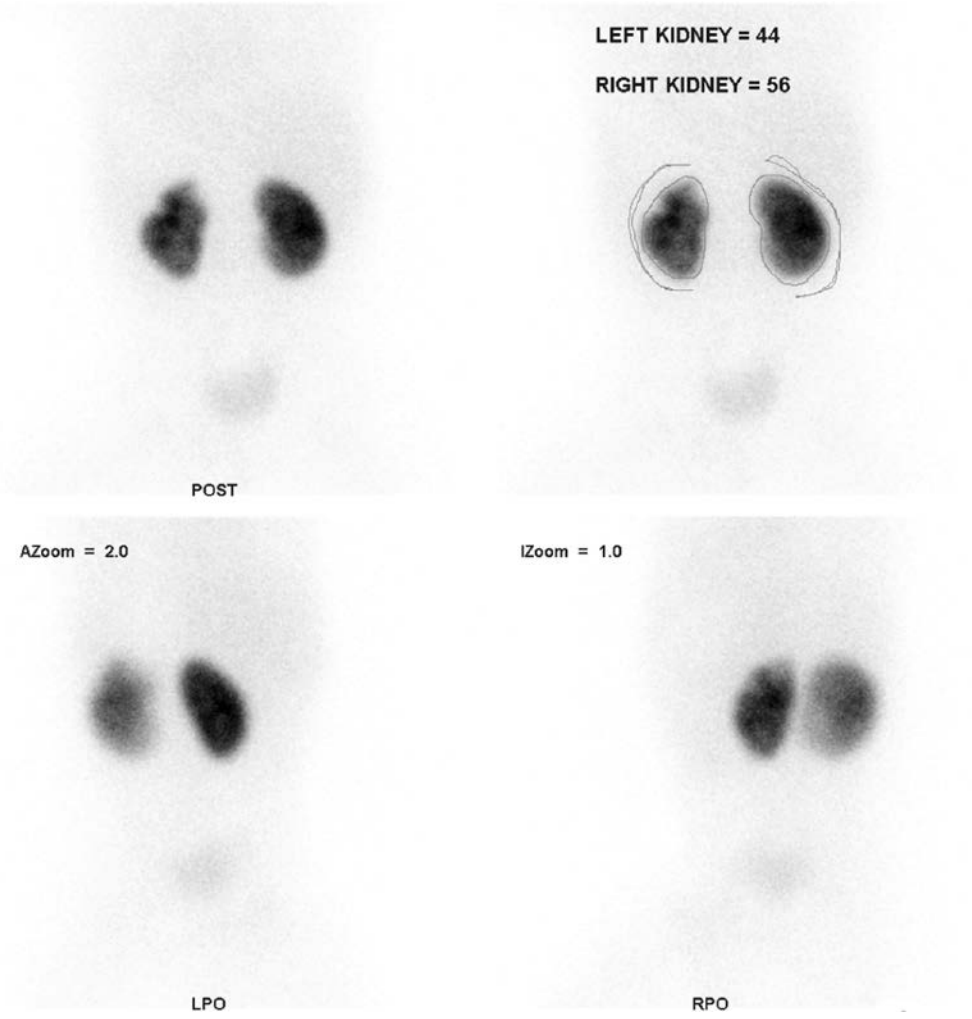


FIGURE 5.6 DMSA renal scan in a 1-year-old male with a history of pyelonephritis and bilateral vesicoureteral reflux shows two foci of cortical defects in the upper and upper lateral region of the left kidney. The posterior differential function is 44% in the left kidney.

as well as to the opposite kidney (Figure 5.10). This is important in deciding whether there is enough function to salvage an abnormal renal segment. Most commonly, the upper component functions less well than the lower one, because of obstruction from an ectopic ureter or ureterocele. Occasionally, however, the lower component of the duplex kidney may have less function, and in this situation, one has to be suspicious of reflux nephropathy of the lower collecting system or ureteropelvic junction (UPJ) obstruction.

Ureteropelvic junction obstruction: The child with UPJ obstruction is usually evaluated pre- and postoperatively for the degree of relative renal function, absolute renal function, and rate of egress of the radioactive urine from the kidneys.

A diuretic renogram permits a quantitative assessment of the effect of surgery and/or postoperative complications on the renal drainage system. However, it should be kept in mind that in children who have had repair of a UPJ obstruction or after reimplantation of the ureters as an antireflux surgical procedure, delays in drainage may persist for several months before eventual improvement.

RENAL TRANSPLANT ASSESSMENT

In children with a renal transplant, the renal scan has been used during the first 2 weeks to evaluate the effectiveness of the transplant surgery. As the renal transplantation techniques have improved significantly, the need for an immediate renal evaluation is not as important. Usually, a renal scan is performed in the first 48–72 hours if the urine output is normal and blood pressure and creatinine (Cr) are as expected. This early renal scan helps us to detect early complications after renal transplant, as well as serves as a baseline study for further comparison. At 2 weeks after the transplantation, the first GFR assessment is performed. Then on a regular basis, the GFR is measured every year. The complications and findings in renal scan are summarized in Table 5.3 (Figure 5.11).

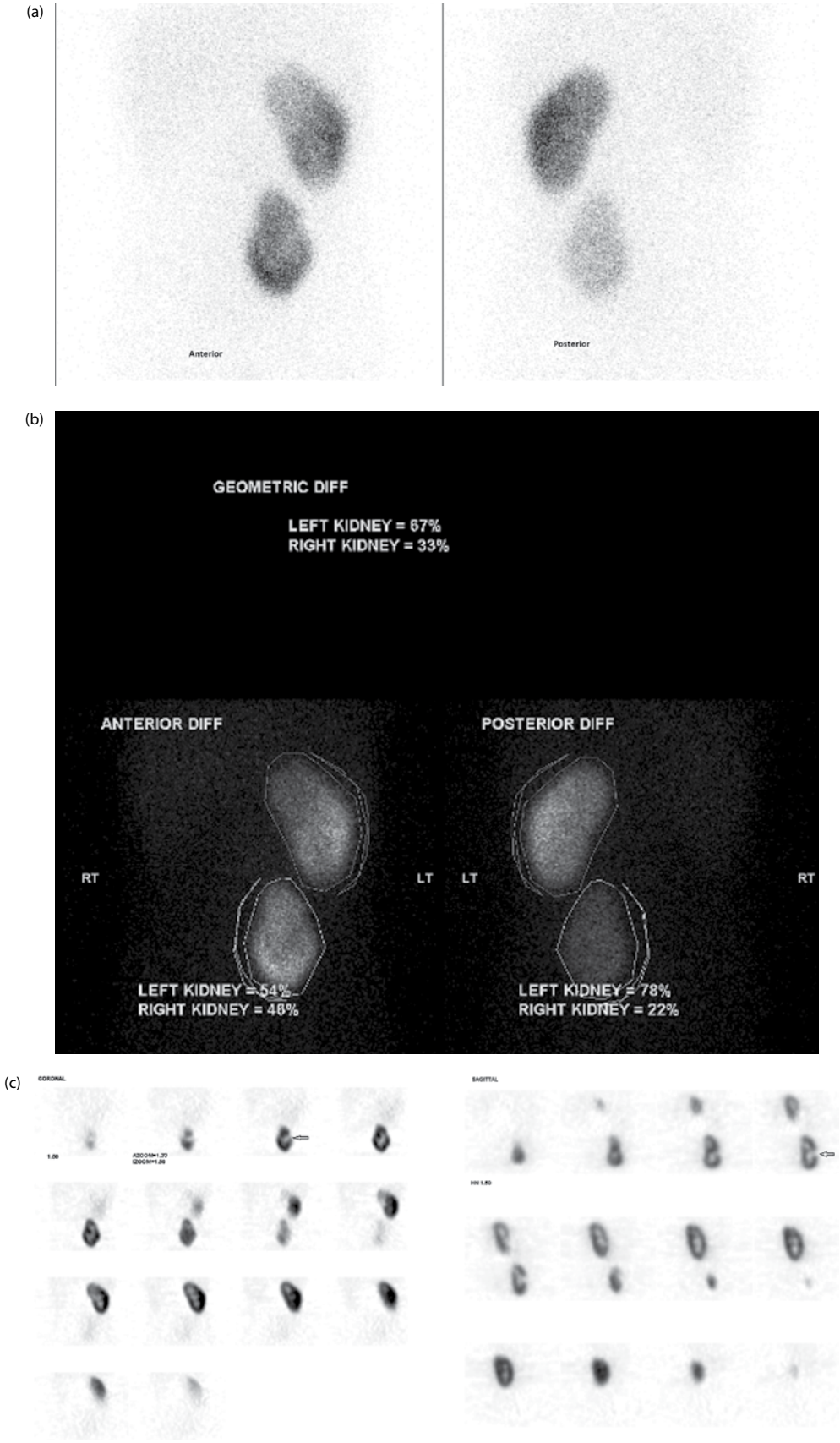


FIGURE 5.7 (a) DMSA renal scan in a patient with an ectopic pelvic kidney. (b) The geometric mean differential function is more reliable than the posterior views to assess the relative function. (c) On SPECT images, there is a focal cortical defect in the ectopic kidney (white arrow), which suggests a scar that was difficult to detect on planar views.

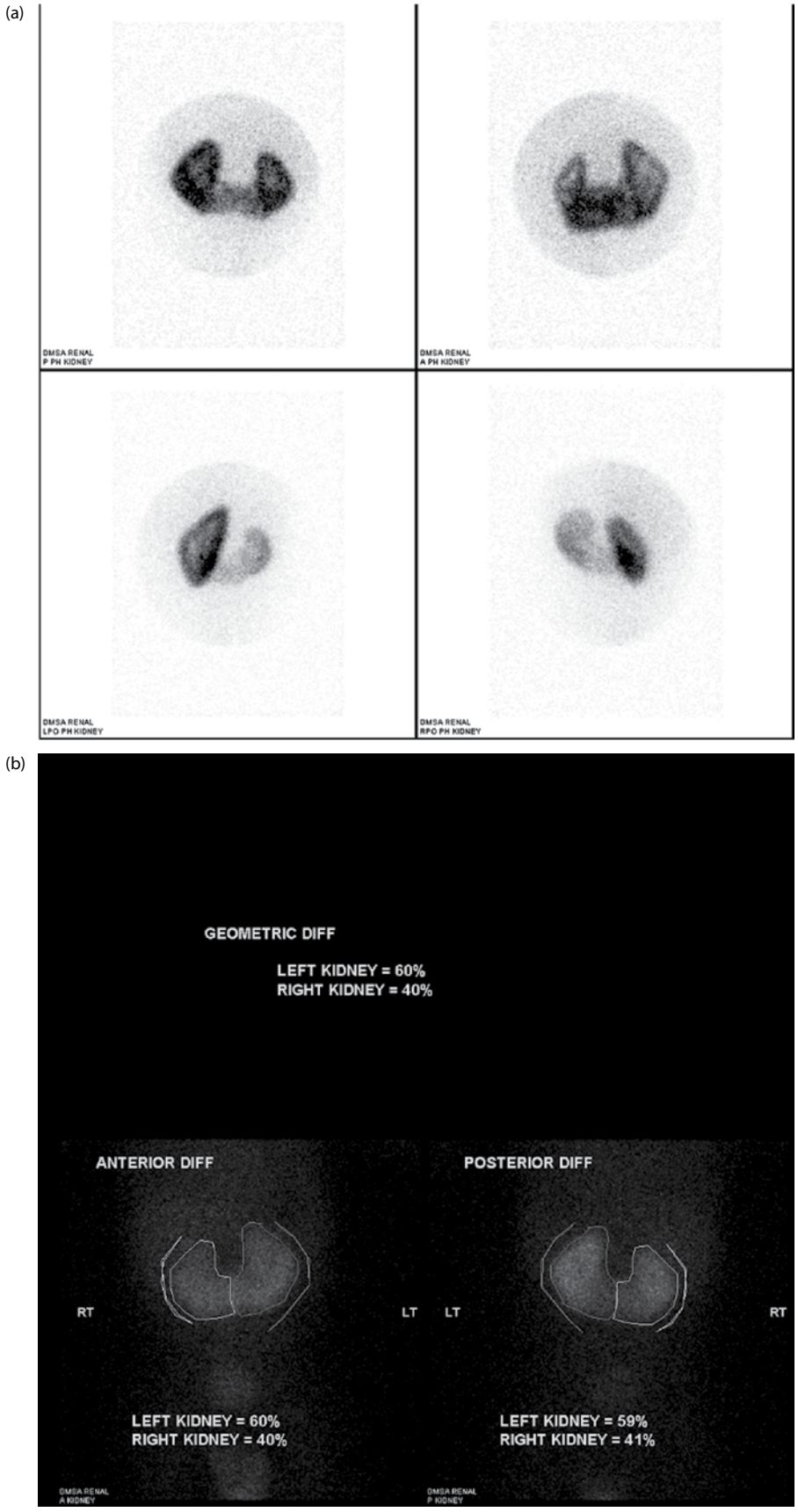


FIGURE 5.8 DMSA renal scan in a 4-year-old boy shows horseshoe kidneys. (a) The presence of fused renal tissue in the midline (isthmus) makes any selection of ROIs arbitrary. (b) In this case, the approximate contribution is 60% from the left moiety and 40% from the right.

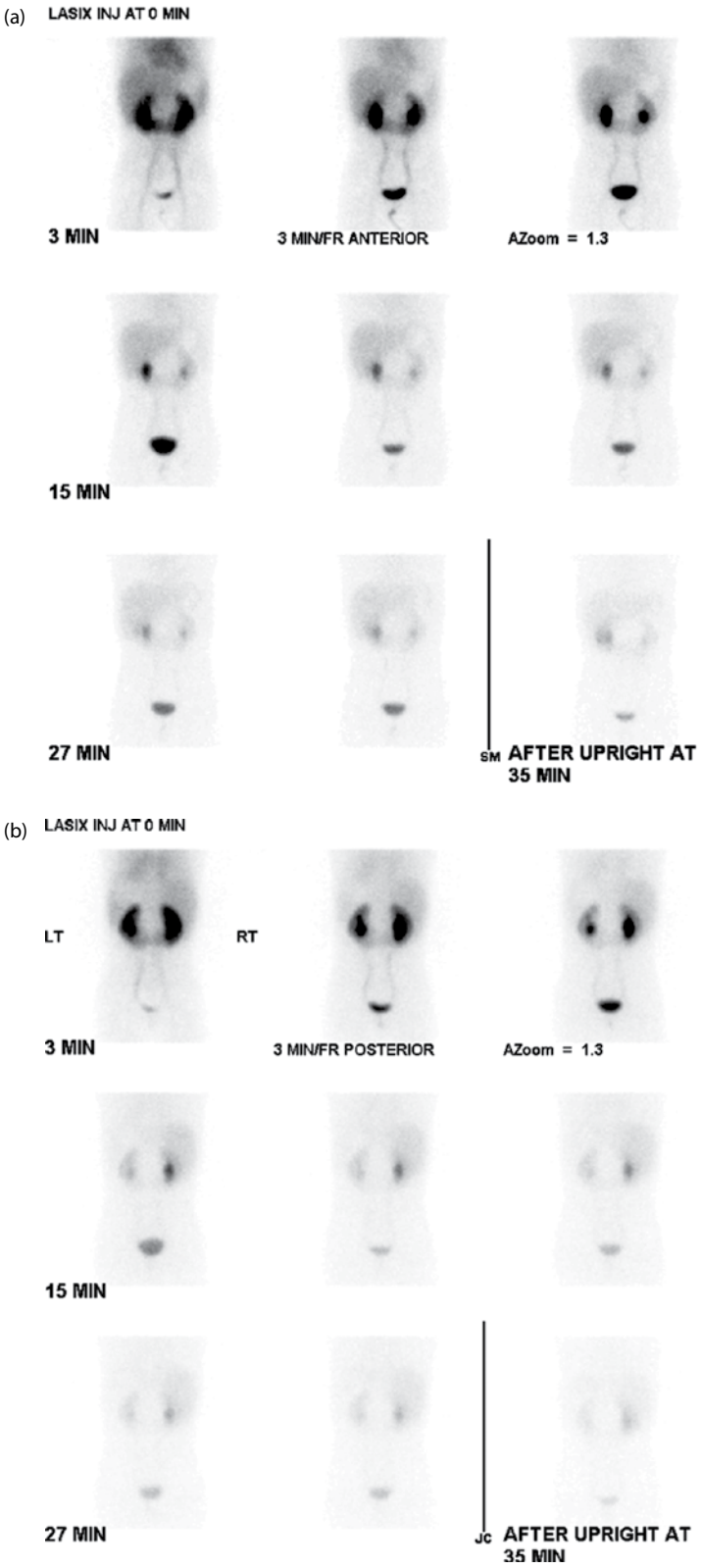
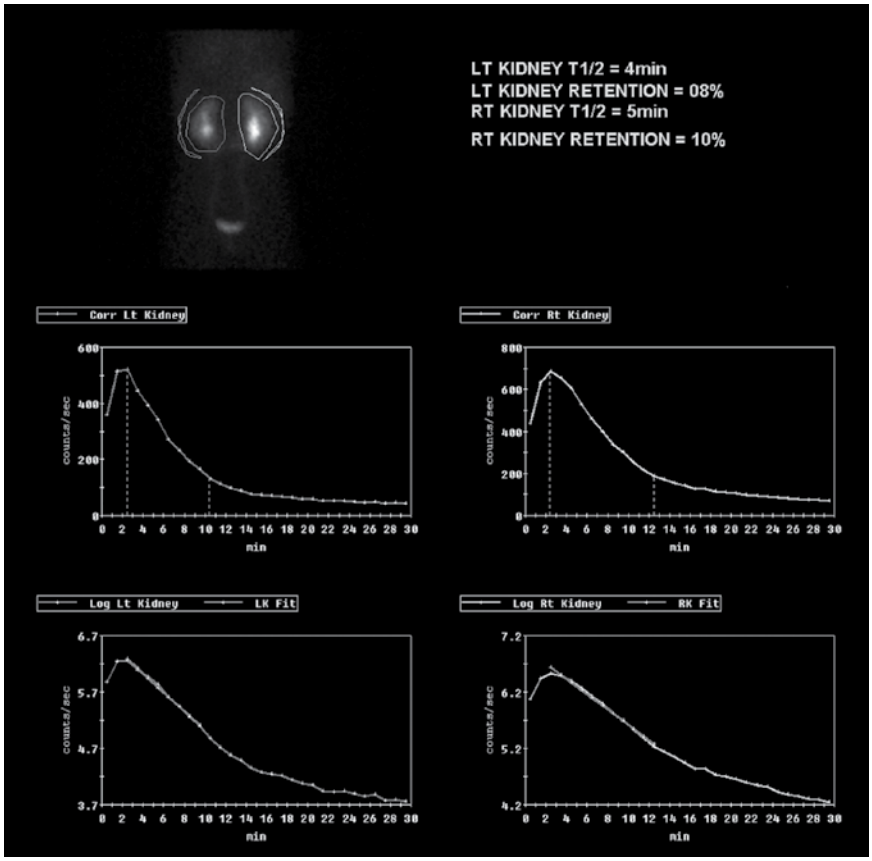


FIGURE 5.9 (a and b) Diuretic renal scan in a patient with horseshoe kidneys shows good uptake of the agent by the kidneys with prominent calyceal systems bilaterally and normal drainage without obstruction. (*Continued*)

(c)



(d)

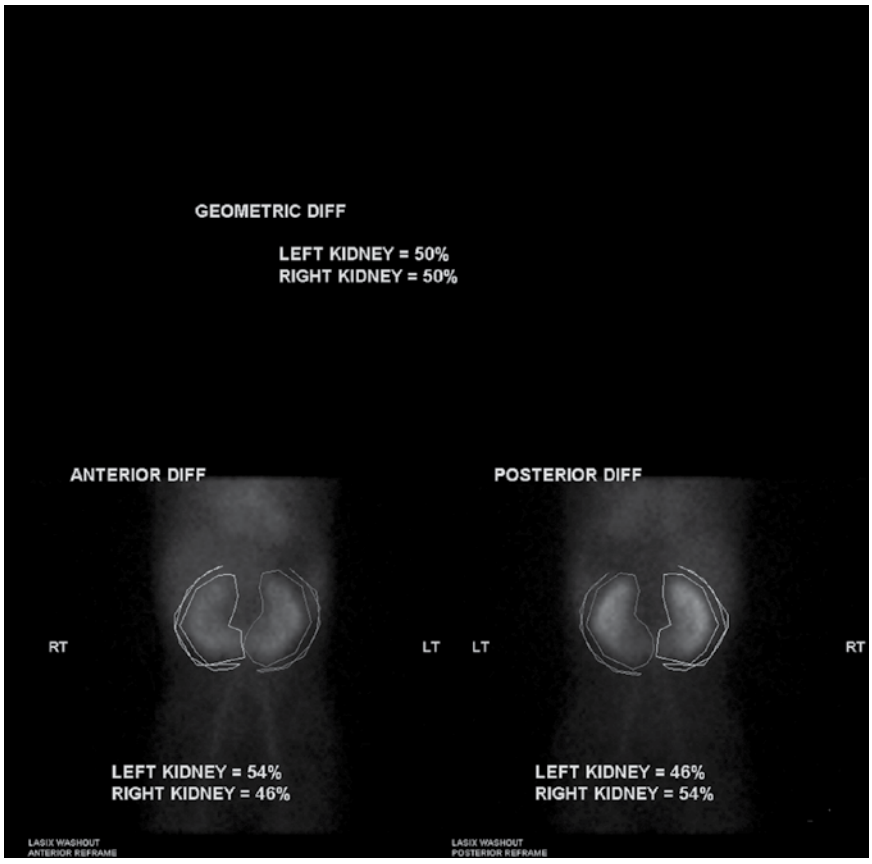
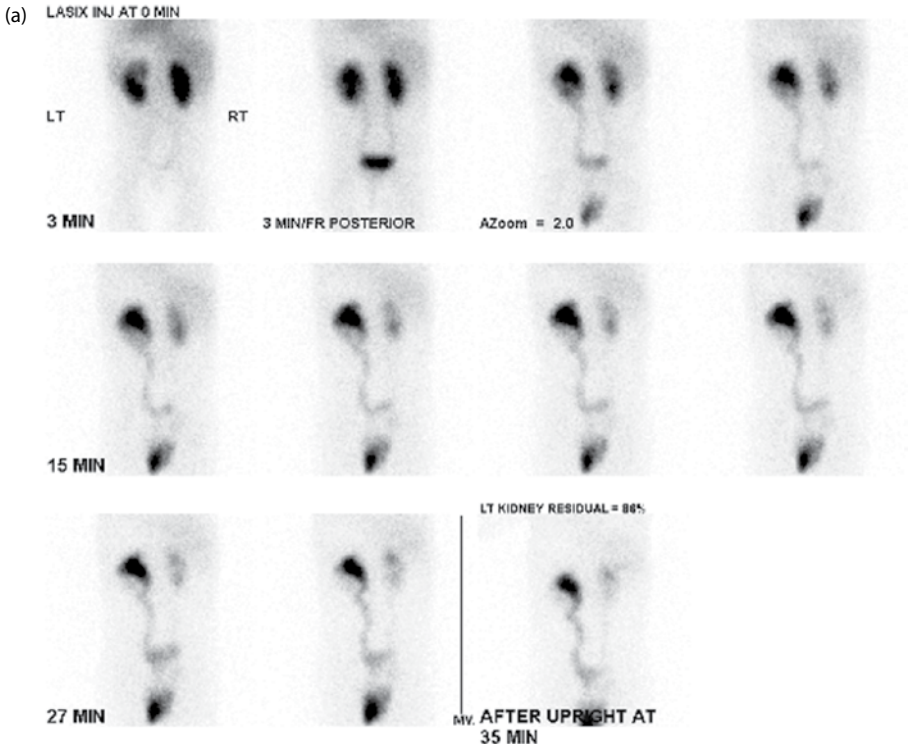


FIGURE 5.9 (Continued) (c) The semiquantitative values are within the normal range with normal renograms (exponential shape). (d) Arbitrary ROIs are drawn over the kidneys to assess the differential function.



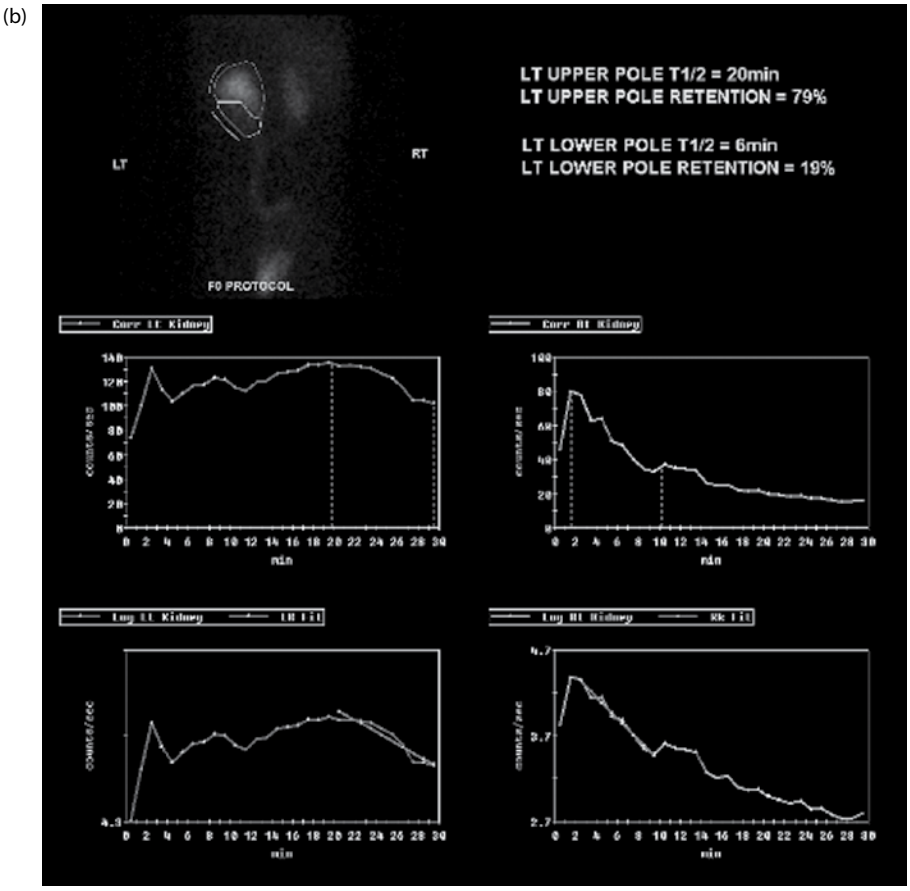
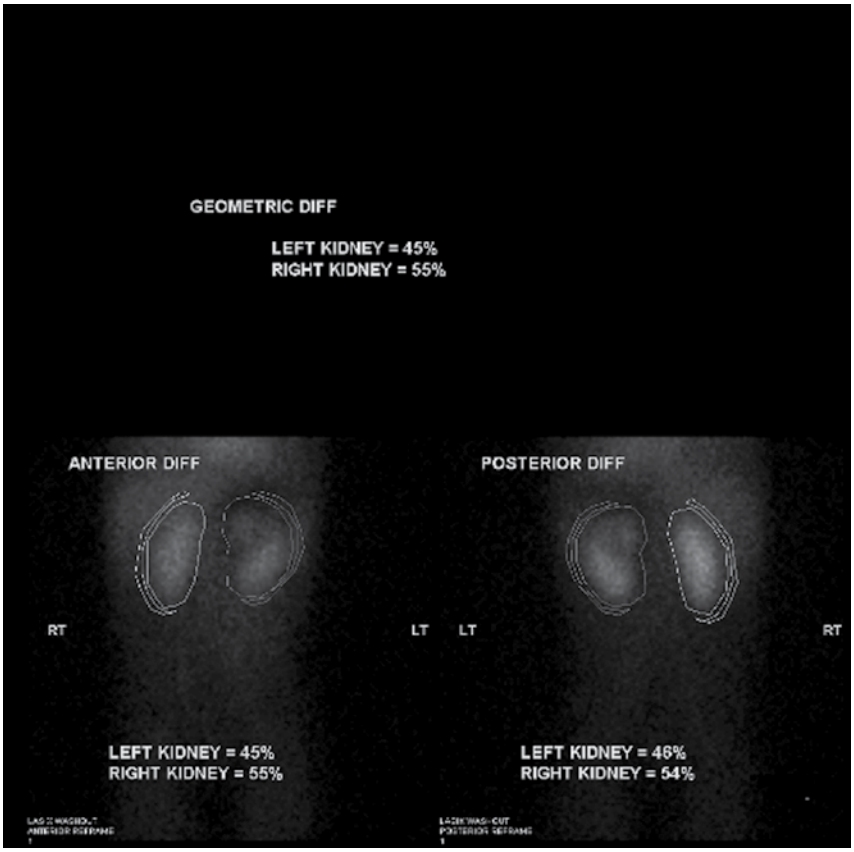


FIGURE 5.10 Diuretic renal scan in a patient with a left duplex system. (a) The lower moiety of the left kidney shows good uptake of the agent with prompt excretion and normal drainage. The upper moiety shows decreased cortical uptake and a dilated pelvicalyceal system. The left ureter is tortuous. The drainage of the pelvicalyceal system of the upper moiety is delayed, which suggests an obstruction. (b) An arbitrary ROI was drawn over the upper and lower moiety of the left kidney. T 1/2 is 20 minutes for the upper moiety and 6 minutes for the lower moiety. (*Continued*)

(c)



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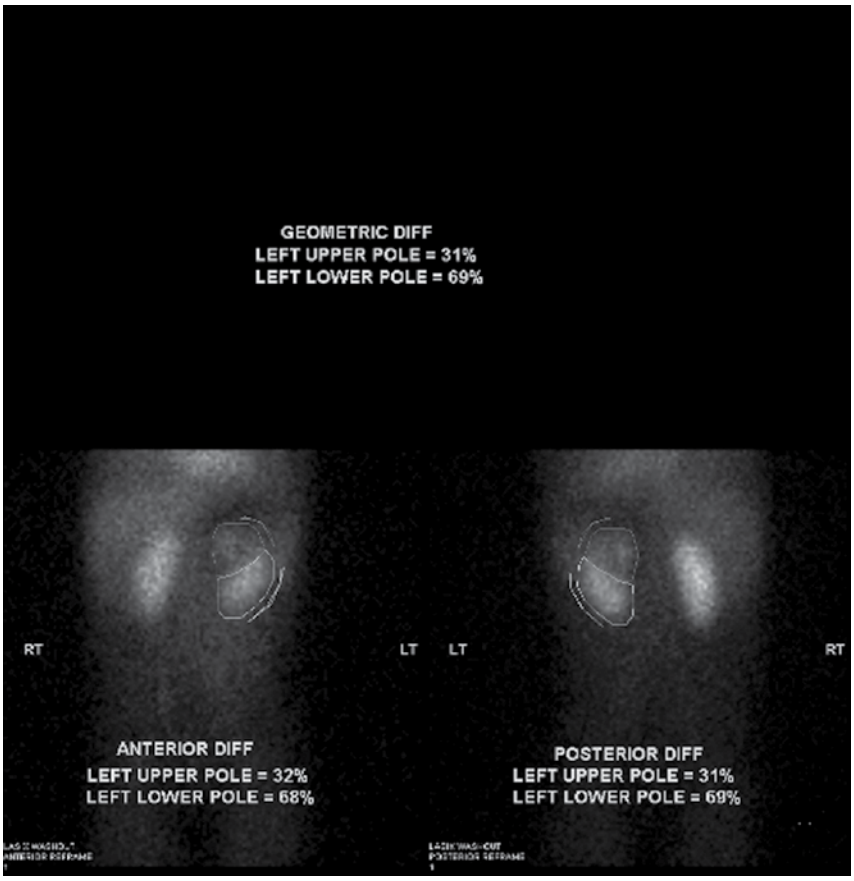


FIGURE 5.10 (Continued) (c) The geometric mean differential function is 45% in the left kidney and 55% in the right kidney. (d) The differential cortical function is 31% in the upper portion and 69% in the lower portion.

TABLE 5.3 Complications of renal transplants

Complications	Nuclear medicine procedure	Findings
Vascular		
Renal artery occlusion	Tc-MAG3 renography	A photon-deficient area at the region of the transplanted kidney
Renal artery stenosis	ACEI renography	Depending on the severity of stenosis, revealed as decreased flow and cortical uptake exaggerated after ACEI
Renal vein thrombosis	Tc-MAG3 renography	Severely decreased or no flow and cortical uptake[a]
Renal		
Acute rejection	Tc-MAG3 renography	Decreased perfusion and cortical uptake with mild retention[b]
Chronic rejection	Tc-MAG3 + ERPF study	Gradual decreased function of the kidney (gradual decrease of ERPF or GFR)
Acute tubular necrosis (vasomotor nephropathy)	Tc-DTPA + GFR study Tc-MAG3 renography	Normal flow but increased cortical retention[c]
Cyclosporine A nephrotoxicity	Tc-MAG3 renography	Similar to ATN, sometimes reduced flow to a lesser degree
Infarcts	Tc-DMSA	Focal cortical defect with volume loss
Others		
Urinary leakage (urinoma)	Tc-MAG3 renography	A progressive abnormal radiotracer accumulation outside of the urinary tract
Postrenal obstruction (calculus, blood clot, stricture, etc.)	Tc-DTPA renography Diuretic renography	Pattern of upsloping or minimal downsloping after lasix injection with increased T 1/2
Vesicoureteral reflux	DRC or IRC	Reflux of the radiotracer into the transplanted ureter and kidney

[a] Due to the lack of collaterals in a transplanted kidney, the effect of renal vein thrombosis on a transplanted kidney is more severe than that on a native kidney.
[b] Acute rejection (AR) may be superimposed on a vascular nephropathy, showing a mixed appearance of AR and Acute Tubular Necrosis (ATN) on MAG3 renography.
[c] A baseline scan is very useful to differentiate between ATN and AR; in AR, usually the baseline study is normal.

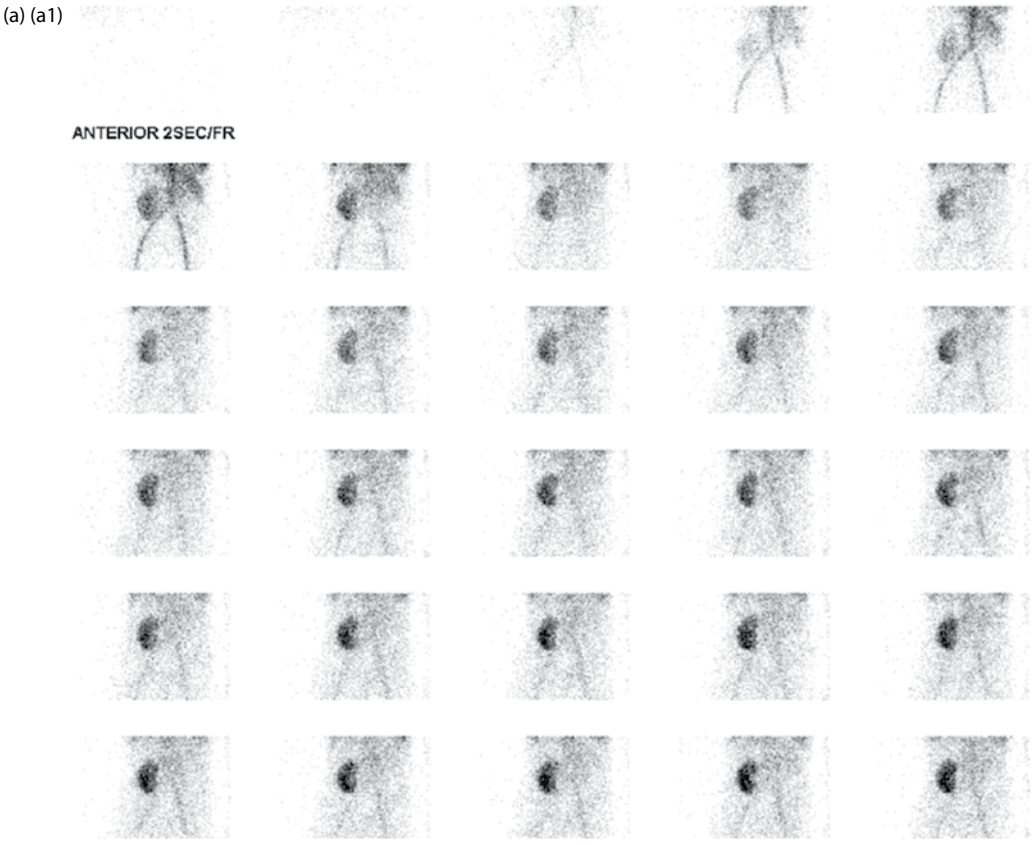
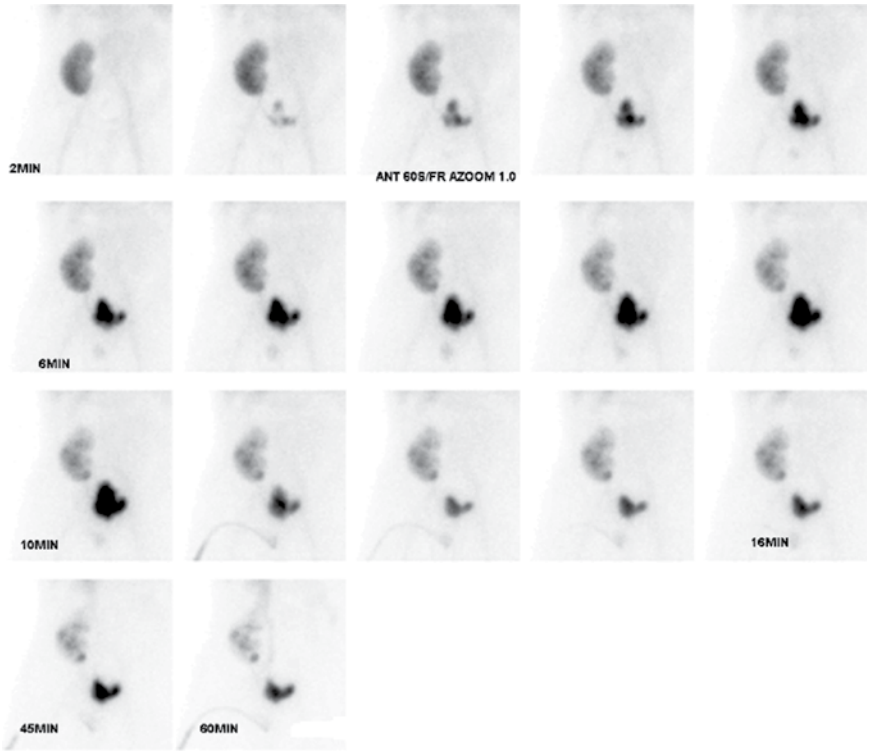


FIGURE 5.11 (a) Renal scan for evaluation of a transplanted kidney on day 1 after transplantation. The study shows normal perfusion (a1). (*Continued*)

(a2)



(a3)

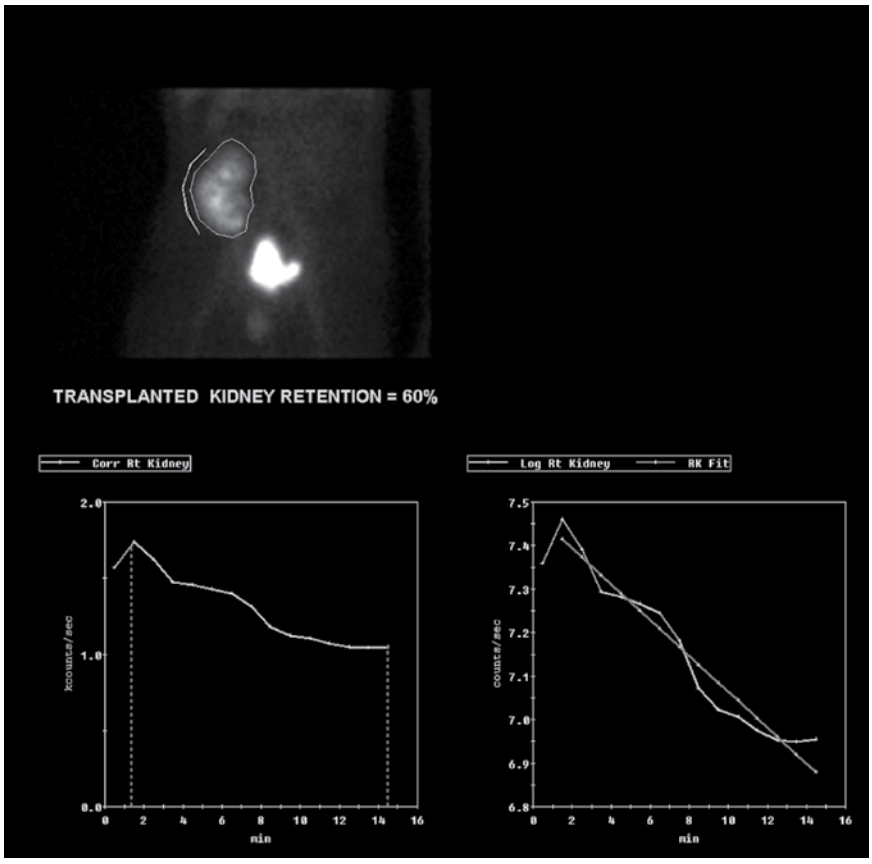


FIGURE 5.11 (Continued) Cortical uptake, excretion, and drainage of the transplanted kidney (a2) with a normal renogram (a3). (*Continued*)

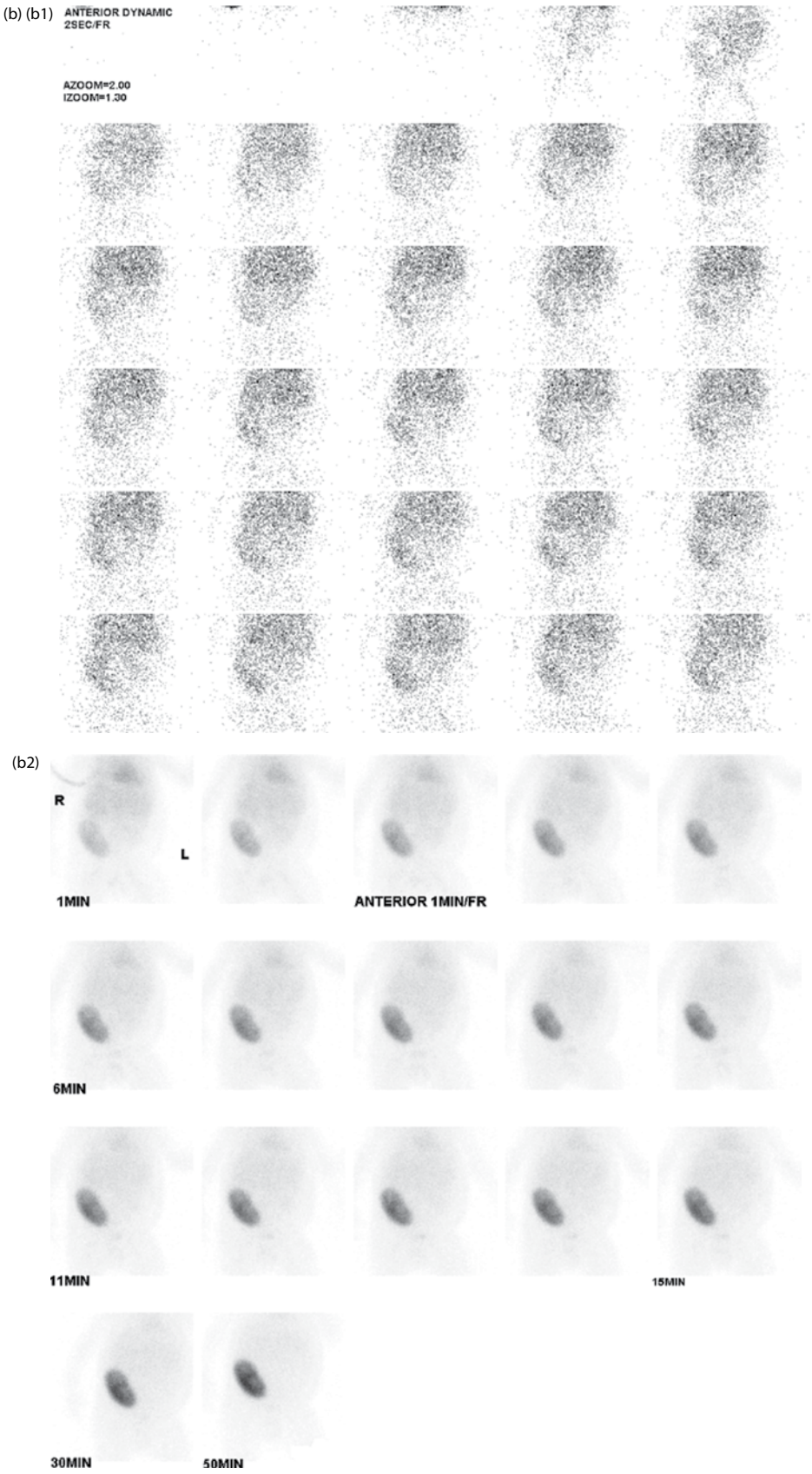


FIGURE 5.11 (Continued) (b) Renal scan for the evaluation of a transplanted kidney on day 1 after transplantation in another patient. The aortic peak activity is decreased and delayed, which suggests a poor bolus of administered radiotracer. In view of a poor bolus, the perfusion to the transplanted kidney appears to be normal or slightly decreased (b1). (*Continued*)

(b3)

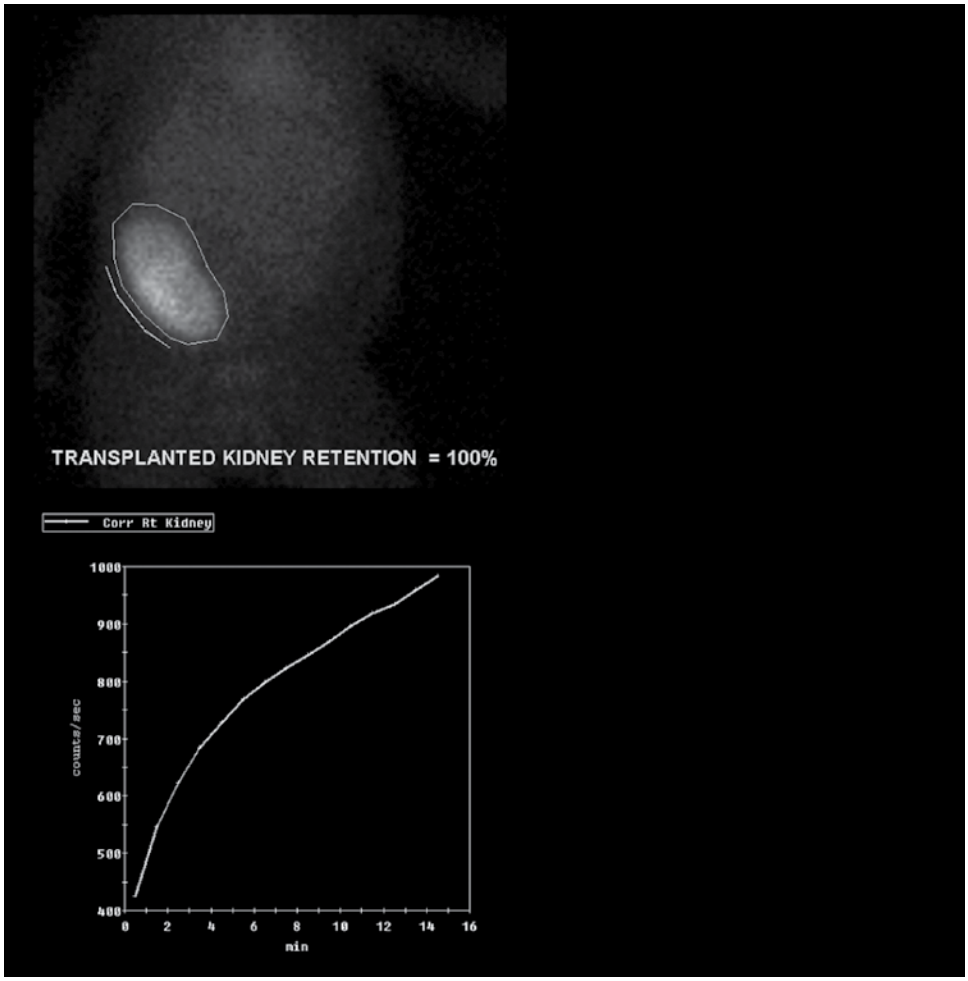


FIGURE 5.11 (Continued) However, there is considerable cortical retention in the transplanted kidney, which suggests acute tubular necrosis (b2 and b3).

KIDNEY TRAUMA

^{99m}Tc-MAG3 renography is a useful method to assess renal function as well as the renal anatomy after either a blunt or a penetrating trauma in a stable patient. Although ultrasound, CT, and IVPs are the common methods for evaluating trauma, sometimes it is important to know the degree of functional impairment. The sensitivity of SPECT ^{99m}Tc-DMSA imaging for renal trauma is very high; it compares favorably to CT and is superior to ultrasound and IVP. Frequently, a band or a section of the kidney with depressed renal function due to fracture is seen (Figure 5.12). Sometimes, a focus of decreased activity may be noted due to a hematoma, which may subsequently subside on follow-up studies.

RENAL ARTERY STENOSIS

Renovascular hypertension constitutes approximately 10% of the secondary hypertension in children. Renal artery stenosis, usually due to fibromascular dysplasia, is the most common cause of renovascular hypertension in pediatrics. When there is a significant artery stenosis, the renin–angiotensin system will be activated in order to maintain the filtration pressure and GFR of the affected kidney. By using the angiotensin-converting enzyme inhibitors (ACEIs), the GFR of the affected kidney will decrease. ACE inhibition renography with Tc-MAG3 or Tc-DTPA is a noninvasive method to evaluate the functioning effects of a stenosis. After using an ACEI, the function of the affected kidney will decrease compared with the baseline study.

The patient should be well hydrated for both pre- and post-ACEI studies. It is recommended to insert an intravenous line for high-risk patients and for the postenalapril study (for instant fluid infusion in the case of hypotension). The patient should be monitored every 15 minutes after the administration of ACEI. Before the study, the patient should discontinue enalapril for 5 days, captopril for 3 days, and diuretics and calcium channel blockers for a few days. It is also suggested to discontinue angiotensin II receptor blockers. However, if the risk of severe hypertension is high, the study may be done without discontinuation of ACEIs, although the sensitivity will decrease.[35] For postcaptopril study, the patient should not eat a solid meal for 4 hours before the study, to avoid any interference with the absorption of captopril.

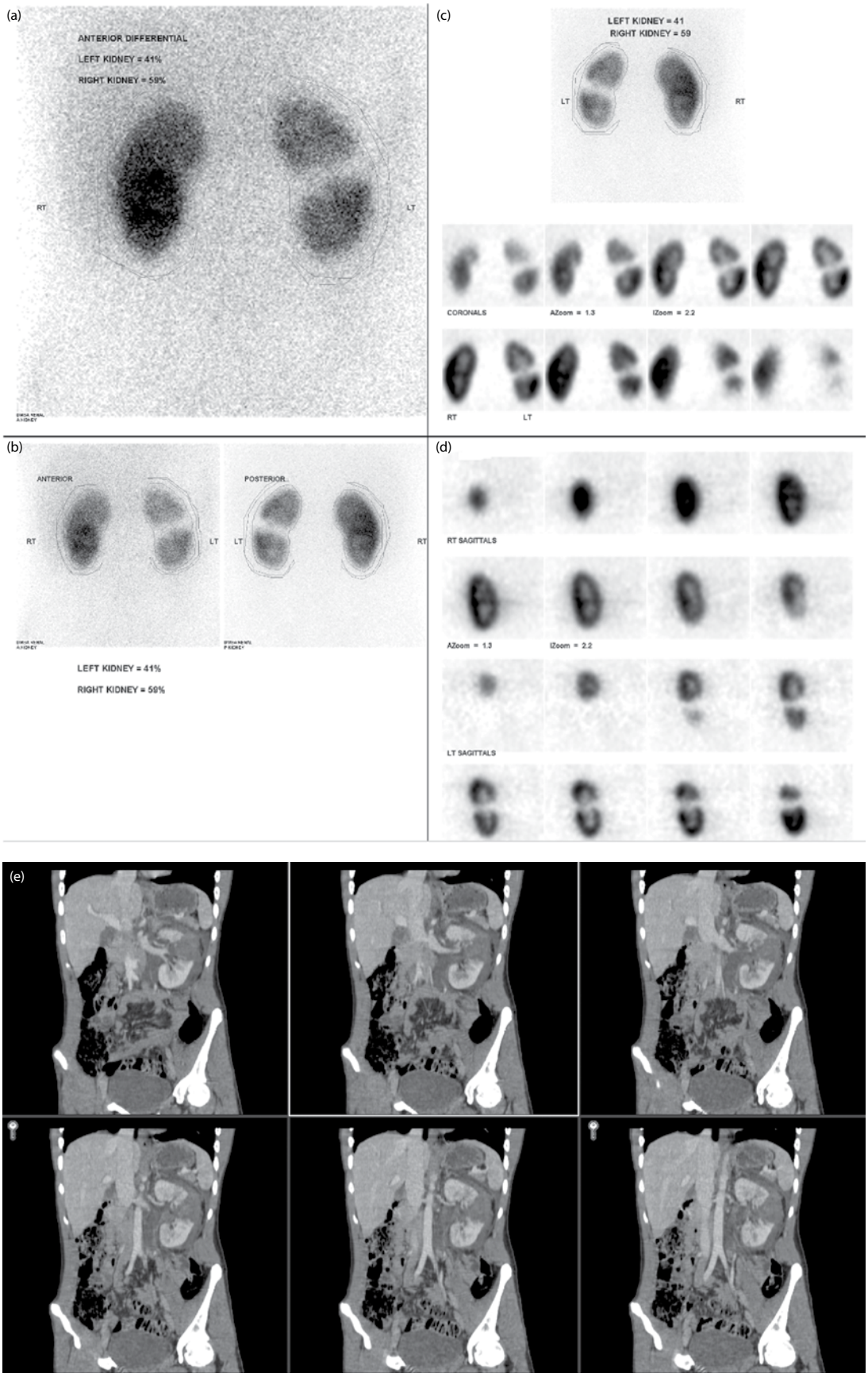


FIGURE 5.12 DMSA renal scan in a patient after a blunt trauma. Planar (a) and SPECT (c and d) views show a band-shaped cortical defect in the left kidney. (b) The differential function is decreased in the left kidney. (e) CT scan coronal views in the same patient.

The pre-ACEI scan is similar to a standard renography. For the post-ACEI study, the same radiotracer is injected either 1 hour after oral ingestion of captopril or 15 minutes after intravenous injection of enalaprilat. It is essential to monitor the blood pressure before the study both for patient safety and to avoid ACEI-induced hypotension that could be a source of a false-positive result. Compared with the pre-ACEI scan, decreased cortical uptake (or decreased GFR) on post-ACEI study with ^{99m}Tc-DTPA is suggestive of hemodynamically significant renal artery stenosis. When using ^{99m}Tc-MAG3, increased parenchymal retention (including increase in the transit time and increase in the ratio of the peak to 20 minutes' activity) and sometimes decreased cortical uptake and delay in the excretion of the radiotracer into the calyceal system, in comparison with the pre-ACEI study, are suggestive of hemodynamically significant renal artery stenosis. In the case of bilateral changes after ACEI, other possibilities, such as ACEI-induced hypotension, and dehydration, should also be considered.

Instances of subsegmental or segmental renal artery stenosis may be difficult to detect by ACE inhibition renography. In these instances, a subsegmental or segmental reduction may be seen on a ^{99m}Tc-DMSA cortical renal scan.

ACUTE KIDNEY LESIONS

Acute kidney lesions are usually related to intravascular hypovolemia with reduced renal perfusion. The extent of the renal damage depends on the severity of the underlying clinical problem. The renal scan (including angiogram phase) is useful in various pathologic states, such as tubular necrosis, cortical necrosis, and renal vein thrombosis. The interpretation of the scan, however, must be made in light of the clinical circumstances, since other entities, such as acute glomerulonephritis, can look somewhat similar.

Children with *acute tubular necrosis* generally show good perfusion to the involved kidney. However, there is delayed excretion because radioactivity is retained within the renal parenchyma, and often no activity is seen in the bladder by 30 minutes. There is no dilatation of the collecting systems to suggest hydronephrosis. In neonates, asphyxiated bladder syndrome may coexist and consists of gross bladder distension with urinary retention. Urate nephropathy of the newborn will look similar because it also causes intratubular obstruction. However, an episode of circulatory compromise is usually present to distinguish acute tubular necrosis.

In *renal vein thrombosis*, depending on the severity and stage of resolution, variable appearance may be seen. Usually, there is a poor perfusion to an enlarged kidney with poor excretion (increased cortical retention). In pediatrics, renal vein thrombosis may be seen as a complication of nephritic syndrome. It is often difficult to distinguish renal vein thrombosis from an arterial problem or intrarenal vascular problem, and this diagnosis should usually be confirmed by contrast angiography or Doppler ultrasound.

MEASUREMENT OF GFR

Measurement of serum Cr or blood urea nitrogen (BUN) is a simple method for the evaluation of renal function. However, renal function has to be reduced significantly before any changes in BUN or Cr are detected. Serum Cr and BUN determination are not so accurate in acute changes of renal function, in different metabolic states, when there are differences in muscle mass, and after some medications. Cystatin C seems to have advantages over serum Cr measurement in pediatric populations. However, it may be influenced by other factors, including weight, height, and serum C-reactive protein.[36]

GFR is the most useful quantitative index of renal function and is used clinically as the gold standard of renal function. GFR can be calculated based on serum Cr level or other serum markers. Different formulas for the calculation of GFR, including Schwartz or Counahan–Barratt, have at least 10%–20% error.[36] Follow-up of patients with impaired renal function requires reliable measurements of GFR. Inuline clearance is the gold standard for the GFR measurement, but it is not practical clinically.

Evaluation of GFR with the nuclear medicine method is accurate and precise. The results are reproducible, so the patients can be followed by this method. Many radiotracers have been used for the evaluation of GFR in nuclear medicine, including ^{125}I-iothalamate, ^{51}Cr-EDTA, and ^{99m}Tc-DTPA. DTPA is the most widely used radiotracer for GFR measurement in North America. In Europe, EDTA is the most commonly used agent. When ^{99m}Tc-DTPA is used, it is possible to do GFR measurement and DTPA renogram study, concomitantly.

There are numerous methods for evaluation of GFR after injection of Tc-DTPA, which are usually categorized into camera-based methods and blood sampling methods. In camera methods, there is no need to do blood sampling and the time of study is shorter; however, it is not as accurate as sampling methods. Radionuclide GFR measurement with blood sampling is used frequently for accurate dose adjustment of chemotherapy (Figure 5.13), for monitoring of drugs that might cause nephrotoxicity, in transplanted kidney for evaluation of rejection, and in assessment of potential live donors for transplantation.[37]

SCROTAL IMAGING

Ultrasound is the method of choice for the evaluation of a painless or chronic scrotal mass. However, in acute scrotal pain, scrotal scintigraphy could be useful to differentiate the underlying pathologies, especially if the result of ultrasound is equivocal. In scrotal scintigraphy after injection of Tc-pertechnetate, sequential anterior static views are obtained for 15–20 minutes after 1-minute dynamic flow images. In *acute torsion*, the early perfusion to the affected testis may be normal, although a small hyperactive focus, a nubbin sign, may be seen proximal to the obstructed vessels. However, on delayed static images, the activity in the affected testis is usually decreased. In a *missed torsion* (delayed torsion), the activity in the affected testis is decreased (infarcted photopenic testis) with a rim of radiotracer accumulation

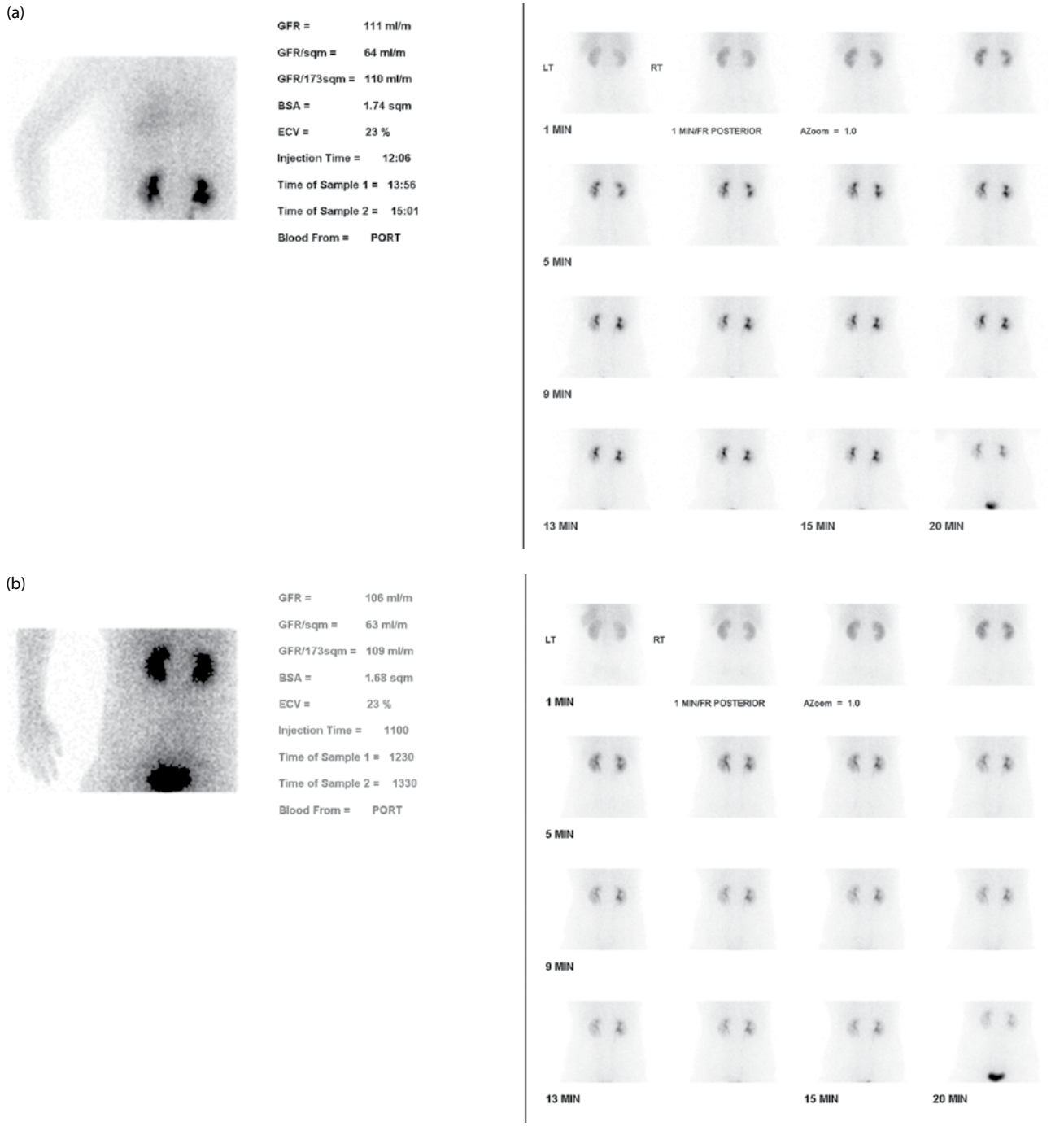


FIGURE 5.13 (a) GFR study in a 14-year-old girl with osteosarcoma of the right leg. (b) Three months after chemotherapy and a high dose of methotrexate, the GFR study was repeated to monitor the kidney function. The GFR values remained unchanged.

due to increased perfusion to the hemiscrotum (a donut pattern). In *epididymo-orchitis*, both perfusion and delayed images show increased activity on the affected side.

NUCLEAR MEDICINE IN GENITOURINARY TUMORS

Advances in molecular oncology, diagnostic imaging, surgical approaches, and stem cell transplantation have improved the survival rate of pediatric genitourinary tumors.[38] Conventional nuclear medicine procedures have an important role in the management of pediatric uro-oncology. The ^{123}I- or ^{131}I-metaiodobenzylguanidine (MIBG) scan has been used for a long time with a high sensitivity and specificity for the detection, staging, and follow-up of neuroblastoma (Figure 5.14). A bone scan is useful when bone metastasis is suspected. It has a complementary role to the MIBG scan in neuroblastoma. When differentiation of a renal tumor versus hypertrophic Bertin columns is of interest, cortical imaging with DMSA is

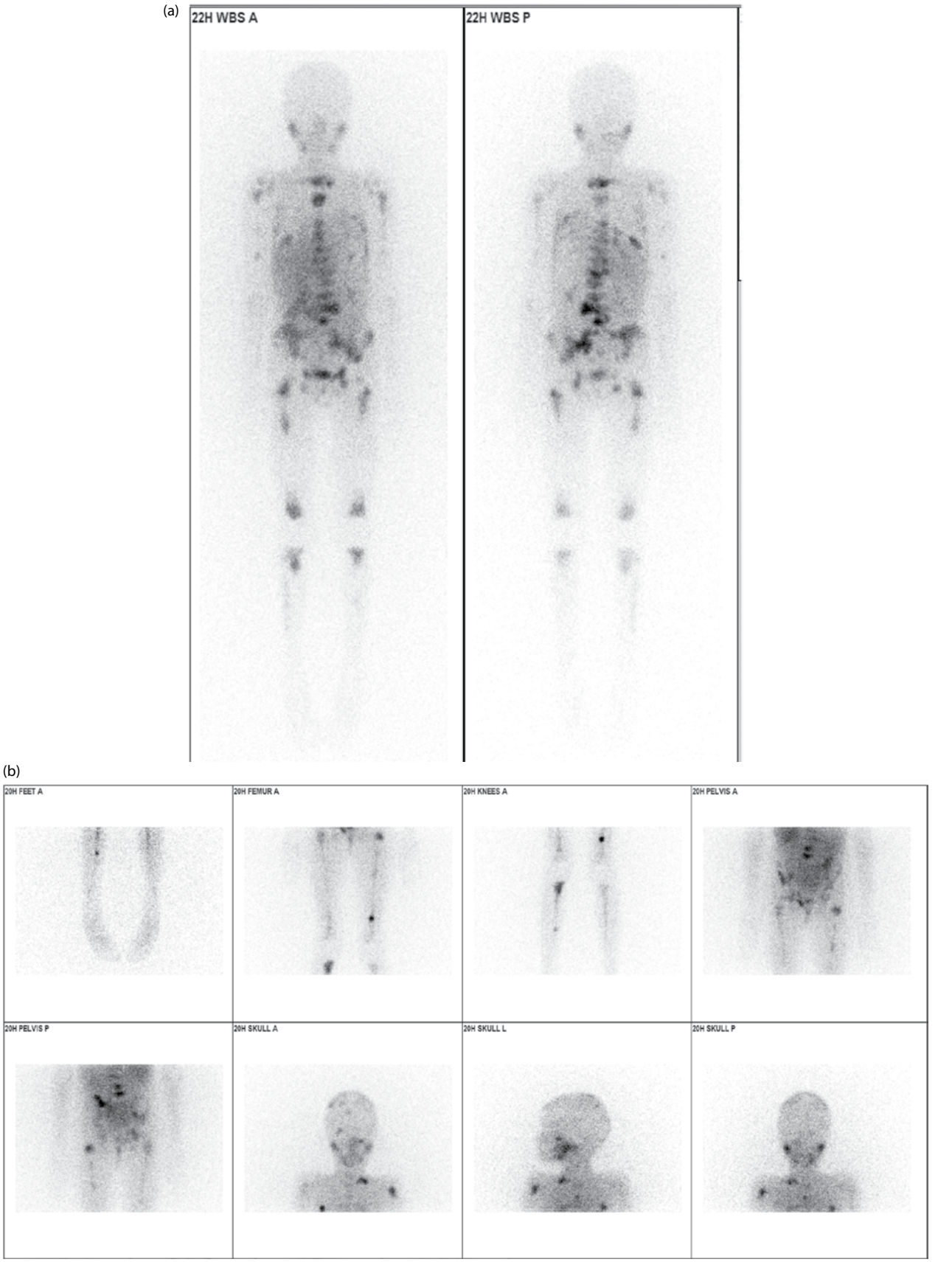


FIGURE 5.14 MIBG scan in a 9-year-old patient. Whole-body anterior and posterior images (a) and spot views (b) show multiple foci of MIBG-avid lesions in the skull, sternum, humeri, ribs, vertebrae, pelvis, femurs, tibias, left supraclavicular lymph nodes, and abdominal and pelvic paravertebral lesions.

helpful. The decision of whether to do a nephrectomy or a reconstructive procedure may be a difficult one, especially in the child whose contralateral kidney is already jeopardized. One of the factors influencing this decision is the degree of function of the affected kidney. A MAG3 renal scan or DMSA cortical scintigraphy can be helpful in this scenario.

The application of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET in pediatric genitourinary cancer is limited. It does not appear to be useful in the initial diagnosis of primary bladder and kidney tumors. However, if the diagnosis of renal cell carcinoma, it is useful to detect the metastasis at the initial diagnosis, staging and restaging, diagnosis of residual renal fossa masses following nephrectomy, and assessment of response to therapy.[39] In testicular germ cell tumors, FDG PET is a very useful method for pretreatment staging and to evaluate posttreatment residual masses. It has a higher diagnostic accuracy than CT for both staging and restaging and should be the test of choice for the assessment of a CT-visualized residual mass following chemotherapy.[39] FDG PET/CT is a valuable tool for initial staging of pediatric rhabdomyosarcoma patients, and seems to be an additional predictor of outcome.[40] New somatostatin receptor PET tracers, such as ^{68}Ga-DOTA-TOC, have very high sensitivity for detection of the neuroendocrine tumors, including neuroblastoma.[41,42] In all kind of tumors, ^{18}F-FDG is valuable to differentiate fibrosis from recurrent disease in the treatment bed, an area of difficulty for CT/MRI.

Neuroblastoma

Neuroblastoma is the most common extracranial solid tumor in infants and children, accounting for 7.6% of all childhood cancers. Approximately half of newly diagnosed neuroblastomas are encountered between ages 1 and 4 years. Despite extensive ongoing clinical and basic science research, neuroblastoma remains an unknown tumor with unpredictable clinical behavior. ^{131}I- or ^{123}I-MIBG is the conventional agent for detection of neuroblastoma with a high sensitivity and specificity. MIBG binds mostly to the presynaptic sympathetic receptors and is actively transported to the intracellular structures predominantly by a type I amine uptake mechanism. As a result, a wide range of over-the-counter and prescribed medications may interfere with the MIBG uptake and should be discontinued before MIBG diagnostic imaging or therapy.[43,44] Whole-body images are obtained 24 and 48 hours after administration of MIBG. SPECT images are also acquired after administration of ^{123}I-MIBG and may help to detect the lesions behind the heart and the liver and better localize the tumor (Figure 5.15). MIBG is positive not only in primary tumor but also in metastatic lesions, including bone

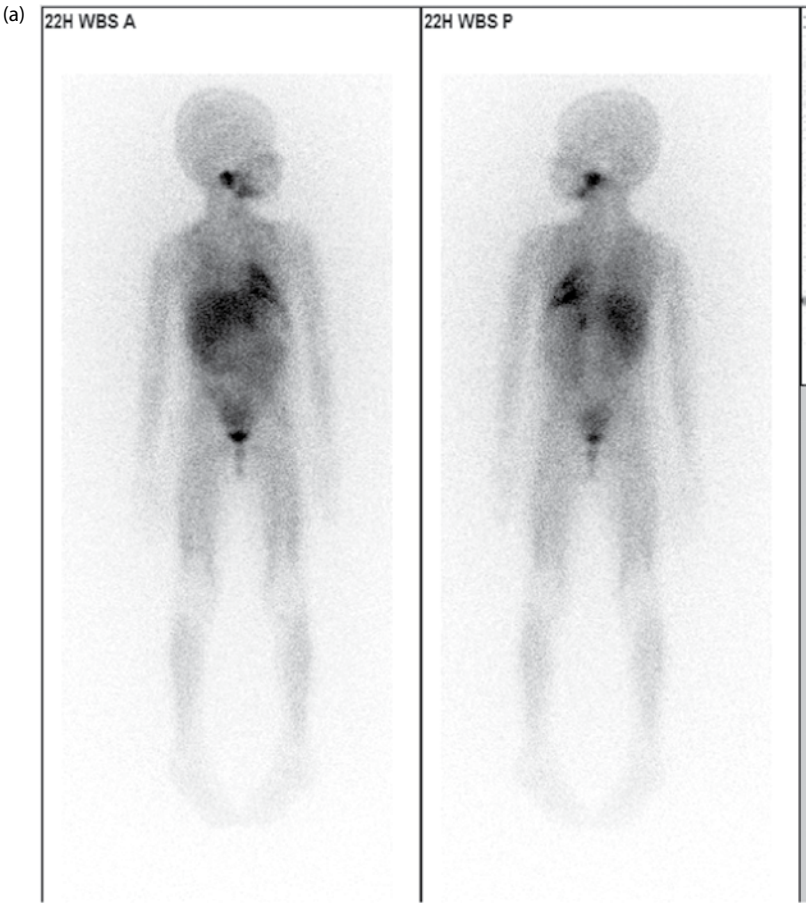


FIGURE 5.15 MIBG scan in a patient with a thoracic neuroblastoma located behind the heart. (a) Whole-body images did not show any abnormality. (*Continued*)

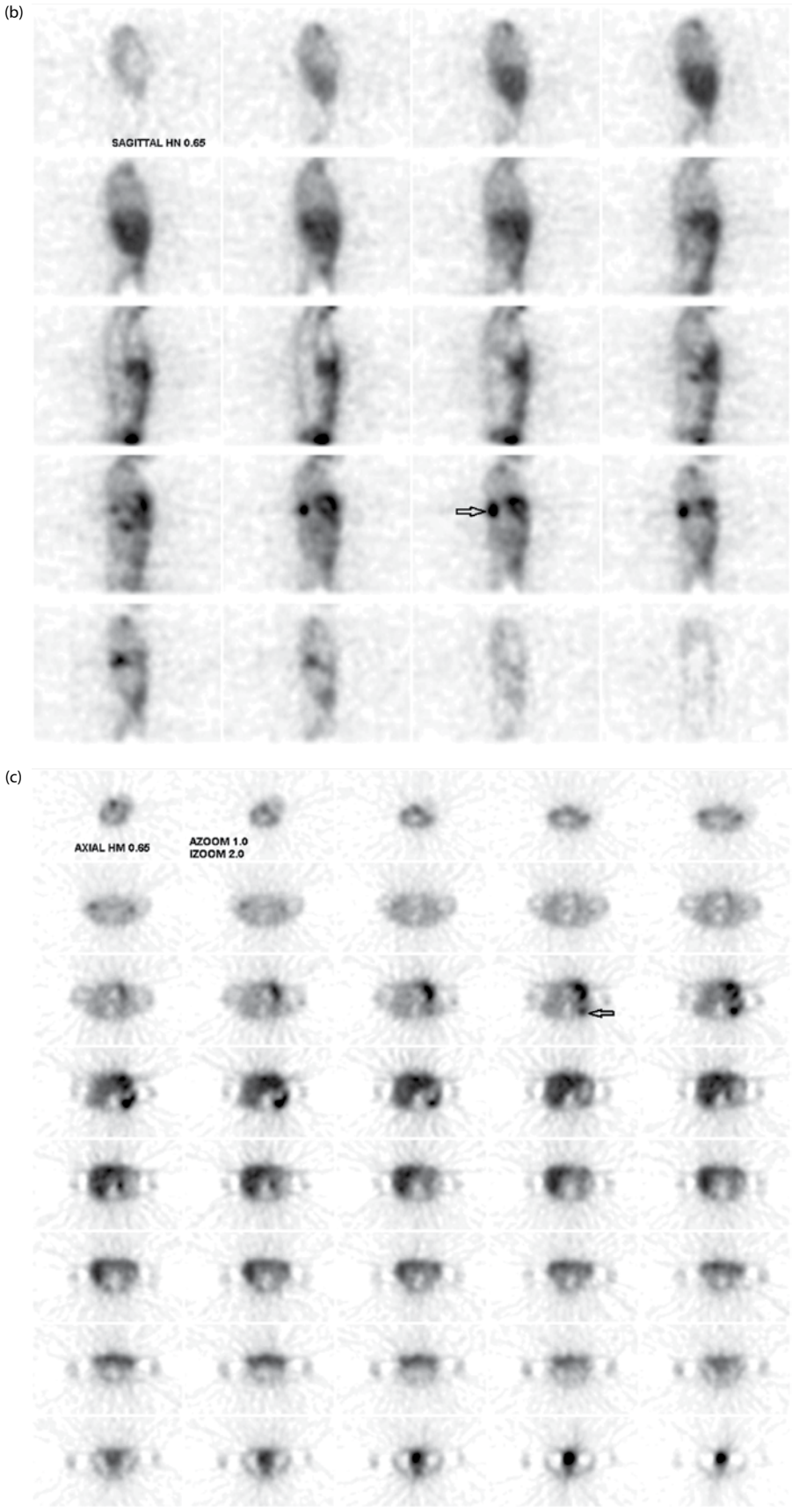


FIGURE 5.15 (Continued) (b and c) On SPECT study, there was a large focus on MIBG activity corresponding to a thoracic mass behind the heart. SPECT study is especially useful in the chest and abdomen to detect the lesions behind or around the organs with physiologic uptake or excretion of the radiotracer.

and bone marrow involvement. The sensitivity of MIBG is higher than that of a bone scan to detect bone metastases. However, in some cases a bone scan may reveal bone metastases that fail to show MIBG uptake. Currently, the MIBG study is indicated for the evaluation of neuroblastoma at presentation, for restaging after treatment, to detect postsurgical residual tumors, for monitoring the effect of treatment, and for early diagnosis of recurrence at follow-up.[45]

Somatostatin receptor scintigraphy (SRS) and ^{18}F-FDG PET are also used for evaluation of neuroblastoma. The sensitivity of SRS (e.g., ^{111}In-octreotide) is higher than that of ^{123}I-MIBG and ^{18}F-FDG in other neuroendocrine tumors. However, MIBG is more sensitive for neuroblastoma. ^{18}F-FDG PET is probably more sensitive when the tumor cells have a high proliferation index (Figure 5.16).[46] Nuclear medicine techniques, including ^{123}I or ^{131}I-MIBG, ^{111}In-DTPA octreotide, somatostatin receptor imaging (^{68}Ga-DOTA-TOC or ^{68}Ga-DOTA-TATE) PET/CT, ^{18}F-FDG PET/CT, and radionuclide therapy with ^{131}I-MIBG, ^{177}Lu-DOTA-TATE, and ^{90}Y-DOTA-TATE, play a major role in the management of neuroblastoma and neuroendocrine tumors.[47]

Wilms' Tumor

Wilms' tumor is the most common childhood renal tumor, accounting for approximately 6% of all pediatric malignancies. The peak age in pediatrics is between ages 1 and 3 years, with 90% of new cases diagnosed before age 7 years. A CT scan of the abdomen has been the standard diagnostic modality. Due to the urinary excretion of FDG, ^{18}F-FDG PET has a limited role in the detection of the Wilms' tumor or differentiation of the tumor from an infectious process. However, it is useful in the restaging of the patients and/or detection of distant metastasis.[39]

FUTURE INVESTIGATIONS

Future directions of renal PET imaging will be the quantitative assessment of renal blood flow with ^{15}O-labeled water, ^{13}N-labeled ammonia, and ^{82}Rb in renovascular hypertension, transplanted kidneys, and drug-induced nephropathy, and the assessment of response to revascularization. The roles of molecular imaging, receptors and oncoproteins, apoptosis, and stem cell kinetics are under investigation.[1,47]

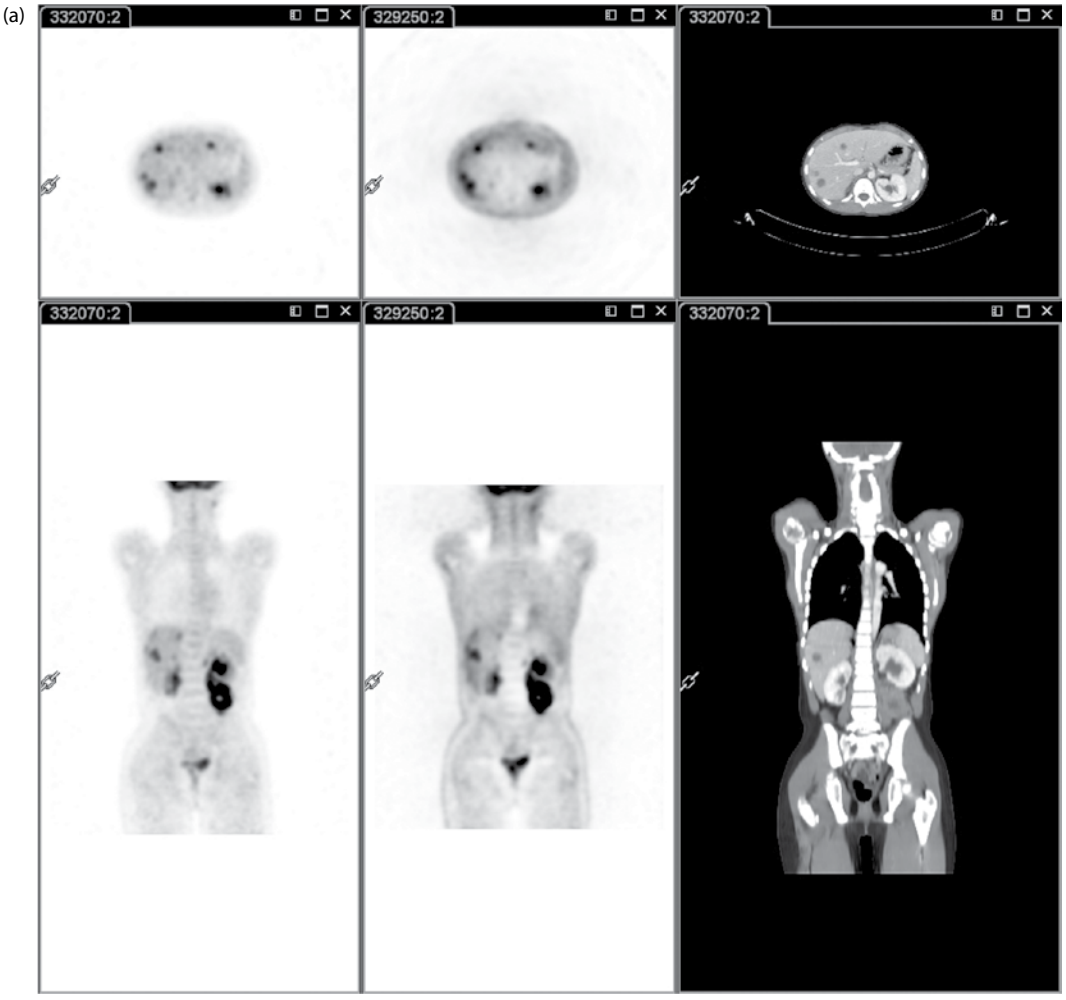


FIGURE 5.16 ^{18}F-FDG PET/CT in a patient with neuroblastoma. (a) axial and coronal PET and CT scans show increased FDG uptake in the abdominal tumor located below the left kidney, and in the liver. (*Continued*)

(b)

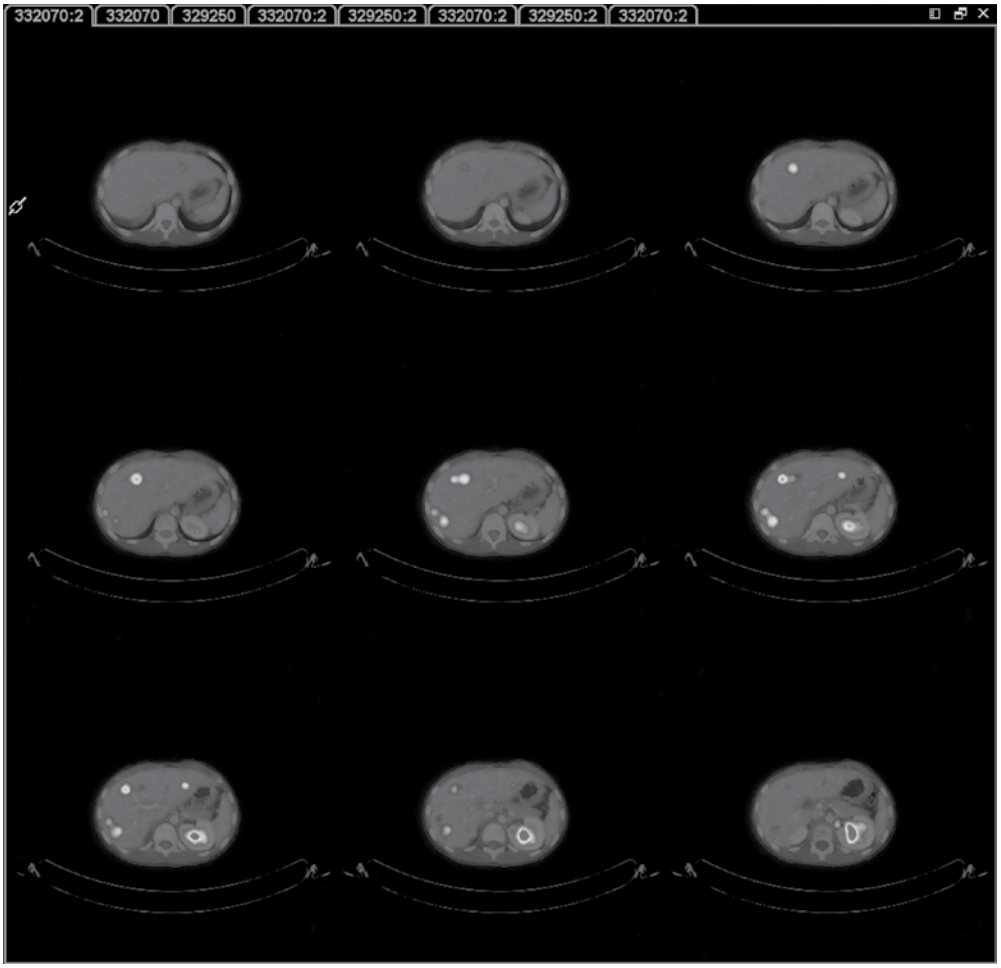


FIGURE 5.16 (Continued) Multiple metastatic lesions in the liver have been better delineated in the axial fused PET and CT scans (b).

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CHAPTER

6

Prenatal and Postnatal Urologic Emergencies

Fernando Ferrer and Patrick H. McKenna

INTRODUCTION

The widespread availability of accurate imaging and genetic screening, and the active participation of pediatric urologists in a multidisciplinary approach to urologic problems have resulted in their detection during fetal development. Consequently, there are few true urologic emergencies since foresight offers the opportunity for counseling parents and planning treatment. As technology and genetic understanding continue to advance, the frequency with which diseases are identified in the prenatal period will continue to increase. These advances have and will continue to present difficult ethical and societal issues to the pediatric urologist, when the abnormalities discovered prenatally are severe enough to warrant consideration of prenatal intervention, possibly even termination of pregnancy. In this chapter, an overview of a variety of urological conditions presenting prenatally and during the first year of life only is offered. An emphasis is placed on information particularly useful to guide the consultative process. We begin by focusing on conditions that might be managed prenatally, and conclude with those for which management must be delayed—or are not recognized—until after birth.

DETECTION OF UROLOGICAL ABNORMALITIES

Routine prenatal ultrasound screening occurs in an obstetrical office using standard two-dimensional (2-D) ultrasound. Inexpensive, readily available, and of high-quality, routine 2-D sonography detects a congenital anomaly in 1%–2% of pregnancies, with up to 20% of these involving urologic conditions.[1–4]

Increasing dilation of the renal pelvis correlates with a greater likelihood of obstruction,[5,6] and in utero progression of mild hydronephrosis is rare, usually less than 15%.[7] Lack of dynamic change in anteroposterior renal pelvis measurement with a change from prone to supine position may also support the diagnosis of significant obstruction.[8] Additionally, increased echogenicity of the renal cortex and decreased amniotic fluid volume have been correlated to impaired postnatal renal function.[9] Findings suggestive of specific diagnoses are provided in Table 6.1. Accurate sonographic imaging may require infusion of fluid into the amniotic space if severe oligohydramnios exists.

However, newer imaging technologies, such as three-dimensional (3-D) ultrasound and fetal magnetic resonance imaging (MRI), are increasingly used to provide greater detail of anomalies identified by 2-D ultrasound.[10] Fetal MRI has expanded its indications and availability but is still expensive and highly specialized compared with ultrasonography. MRI can provide additional anatomic detail that may facilitate prediction of future renal function,[11] especially when oligohydramnios impairs ultrasound quality.[12–16] When anatomy is complex or standard sonography is inconclusive, MRI has been found to change management in up to 33% of cases.[17,18]

Ultrasound still has limitations,[19] and fetal MRI is an emerging modality for evaluating prenatal urologic conditions and associated anomalies.[17,20] Fetal MRI may be particularly helpful when amniotic fluid levels are low or to provide additional prognostic information on renal function.[12–16] Any imaging must be considered in light of other factors.

When the urological condition has been identified only after birth, physicians need to consider the unique aspects of bonding between the infant and the parents.[21–23] Bonding can be negatively impacted by the abnormality itself and by any undue separation of the infant from the parents.[24–26] Prenatal counseling may aid in bonding.[23] These considerations should impact the treatment of infants with and without obvious congenital abnormalities. The support should extend beyond helping the family understand the anomaly, and should include managing parental fears concerning job loss, financial difficulties, and effects on other family members.[24] Early discharge of infants who can be adequately managed as outpatients is

TABLE 6.1 Prenatal ultrasound findings suggestive of specific diagnoses

Round symmetrically thick-walled bladder	Complete urethral obstruction (atresia or PUV)
Elongated/tubular bladder, symmetrically thick wall	Partial urethral obstruction (stricture or PUV)
Elongated/segmented or “snowman” bladder	Urethral hypoplasia (i.e., prune belly syndrome)
Dilated proximal urethra or keyhole sign	PUV, or possibly more distal lesion

encouraged. When prolonged hospitalization is required, parental rooming in with the infant is encouraged. A psychiatrist and staff educated on bonding issues should be actively involved in patient and parental management.[27–30]

PRENATAL INTERVENTION

Although still rare, the incidence of prenatal surgical intervention, including medical treatment, termination of pregnancy, early induction of delivery, and surgical intervention, is increasing. There are complex ethical, technical, and medical issues surrounding all forms of prenatal intervention.[31–33] These issues are especially important in countries such as the United States, where there is a time limit on the gestational age when elective termination can be performed. However, even in countries with few legal restrictions on termination throughout pregnancy, accuracy of the prenatal diagnosis and a correct explanation of the long-term outcomes are foundational to informed decision making.[34] The difficult task is providing an accurate assessment of the quality of life for patients with severe congenital abnormalities so that parents can make an educated decision about intervention or pregnancy termination. Many centers have established multidisciplinary teams comprised of dedicated providers representing maternal–fetal medicine, pediatric anesthesia, pediatric surgery, pediatric radiology, pediatric urology, and pediatric nursing to adequately address the full scope of care for the mother and child.[35]

The conditions pertinent to a pediatric urologist most likely to be considered for prenatal intervention include lower urinary tract obstruction (LUTO), congenital adrenal hyperplasia (CAH), and open neural tube defects. The flow diagram in Figure 6.1 is designed to focus on the importance of oligohydramnios when considering intervention. If the flow diagram is followed, few patients will be considered for prenatal intervention. The remaining conditions, while increasingly diagnosed prenatally, are treated after birth.

COMPLICATIONS OF PRENATAL INTERVENTION

Intervention in the prenatal period can take various forms, from medical treatment to surgical intervention. The consequences of prenatal medical treatment for CAH exemplify some of the ethical and practical problems with prenatal

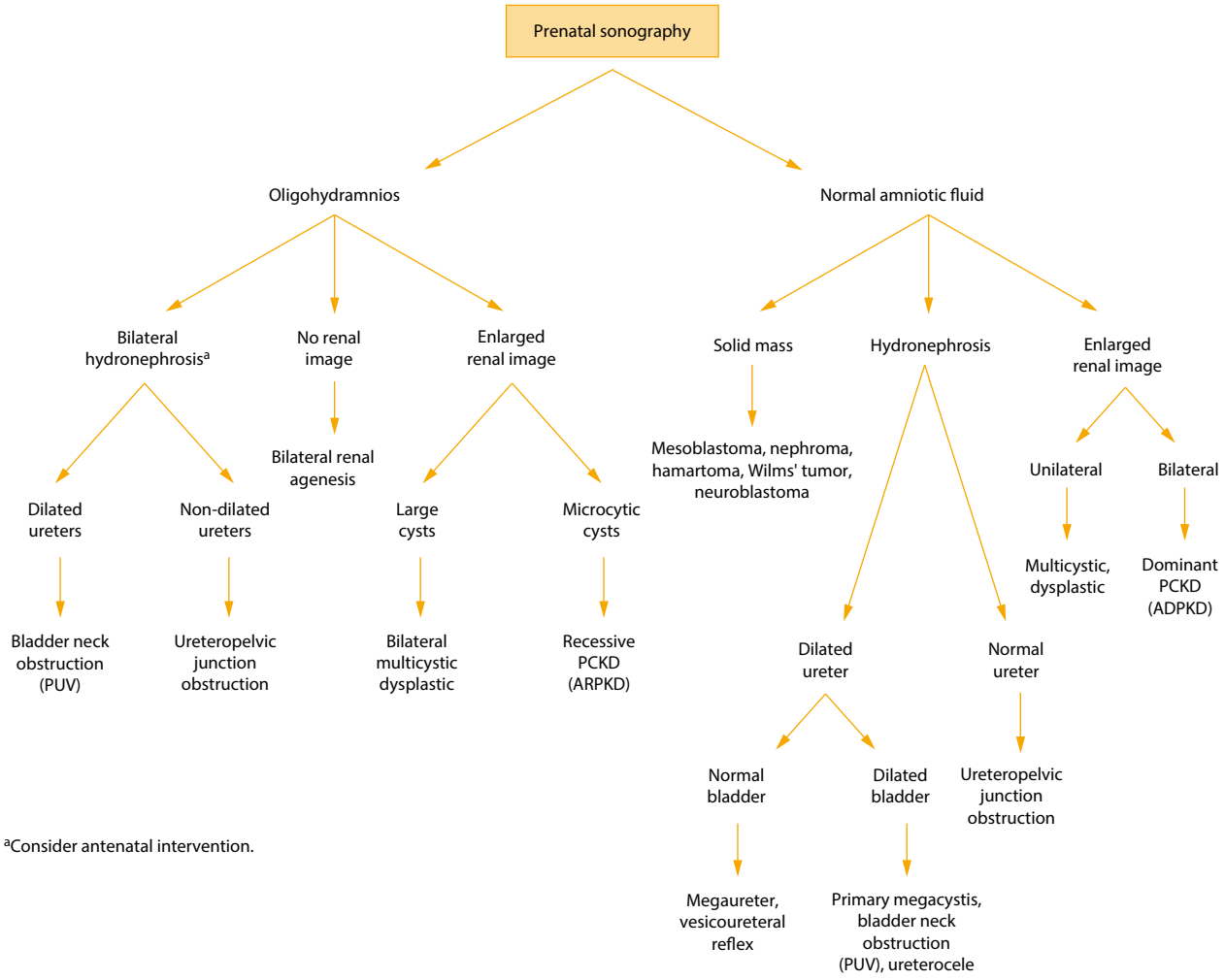


FIGURE 6.1 Prenatal flow diagram. PCKD, polycystic kidney disease.

treatment of the fetus with medication and are discussed in that section of this chapter. The risks to the fetus escalate the more invasive the form of prenatal intervention.

Minimally invasive procedures, such as amniocentesis, are often needed to establish a diagnosis and may need to be repeated during pregnancy. Amniocentesis during the second trimester has become almost a routine procedure. When it is done with ultrasound guidance, there is a 1% incidence of spontaneous abortion.[36–38] Fetal hemorrhage, cord laceration, direct fetal injury, uterine injury, chorioamnionitis, amniotic fluid leak, and talipes equinovarus (club foot) have been reported after amniocentesis. But, when amniocentesis is performed using specific guidelines by experienced teams, these risks are minimized.[39–41]

Chorionic villus sampling (CVS) historically had a fetal loss rate of approximately 3.5% and infection rates of 0.25%–0.5%, although a recent review shows rates similar to those for amniocentesis.[36,42,43] Very early CVS, around 7 weeks' gestational age, carries an increased risk of fetal limb reduction defects of 1%,[44,45] but by 10 weeks, the rates equal those of the general population.[43,46] Recent data suggest that CVS may be safer than early amniocentesis,[47] and current consensus supports CVS as the preferred option prior to 13 weeks.[48,49] In recent years, screening protocols combining maternal age, fetal ultrasound, and serum markers, such as β-human chorionic gonadotropin (β-hCG) and plasma protein A, have led to a reduction in the use of invasive testing.[50] This trend will likely continue as more accurate noninvasive testing is developed.

More invasive intervention, including percutaneous procedures and open surgery, are associated with more significant problems. The main urological abnormalities currently considered for intervention include fetal urinary tract obstruction and myelomeningocele repair.[51,52] Even the most invasive procedures have minimal maternal risks or effect on future maternal fertility.[53] Common complications of prenatal urologic intervention by hysterotomy or percutaneous access include uterine contractions with premature delivery, chorioamnionitis, fetal or maternal injury, and fetal loss, in addition to any procedure-specific risks, such as shunt migration.[54–56] The increased use of percutaneous laparoscopic surgery with or without robotic assistance may decrease the problems of uncontrolled uterine contractions. However, laparoscopy carries the risk of percutaneous access wounds, including injury to other fetal organs and to the abdominal wall.[57–66]

Development of better tocolytic agents and other methods to prevent uterine contraction is crucial to successful prenatal surgery. New research into changes on the cellular level after fetal intervention may help guide therapy to prevent complications.[67] Once intervention is anticipated, the pediatric team, including the maternal–fetal obstetrician, pediatric urologist, and neonatologist, should be available because complications such as uncontrolled uterine contraction or serious fetal injury may require immediate delivery, infant resuscitation, or surgical intervention.[68]

TERMINATION OF PREGNANCY

The increased detection of fetal anomalies has led to increased rates of termination of pregnancy for fetal anomalies (TOPFA).[69] A broad spectrum of prenatally diagnosed conditions may lead to a decision to terminate the pregnancy, including severe genetic defects; universally fatal conditions, such as anencephaly or isolated structural (i.e., cardiac) or mental (i.e., Down's syndrome) conditions; or conditions with late-term morbidity, such as Huntington's disease, while urological conditions are rarely among reasons for TOPFA. When encountered, prenatal counseling for severe urological conditions must also consider the long-term quality of life issues against the ethical, psychosocial, and medical risks for TOPFA.

Rates of TOPFA increase according to the severity of the condition.[70,71] There are significant differences in rates of TOPFA, particularly late-term TOPFA (occurring after 22–24 weeks' gestational age) between countries, as well as regional differences within countries.[69,72] France has the highest rate of late-term TOPFA at 2.65 per 1000 live births, which is likely influenced by the accessibility of prenatal screening and greater legal acceptance of late TOPFA compared with other countries.[72] Religious and socioeconomic factors also have a significant impact on patient and provider views regarding TOPFA.[70,73]

The ethical and moral issues surrounding TOPFA are complex, and many are unique, as prenatal medicine is the only field in which termination is presented as a treatment option.[74] Nearly one-third of prenatally detected abnormalities may not be detected until near or after the gestational age limit for legal abortions of 22–24 weeks.[75] This leaves parents little time when faced with this difficult decision. The legal framework surrounding TOPFA late in pregnancy varies greatly by country, but there is a general trend toward increased legalization.[76] Many of the current laws and professional guidelines were set before current diagnostic techniques, and a significant number of laypersons and medical practitioners feel that they are inadequate today.[77–80]

Termination of a pregnancy carries great potential for psychological and emotional stress for the parents and medical staff involved. Postpartum depression can occur in up to one-third of patients, three times the expected rate after an uncomplicated birth, and are higher in younger women.[81] Many women feel inadequately prepared regarding the various choices they would have to make and the potential difficulties that may be encountered during the process.[82] Physicians themselves report that they often do not address difficult issues, such as the possibility of feticide or that the fetus may survive the procedure.[34] Fetal survival of the termination procedure can be a particularly distressing scenario, and medical personnel need to be prepared for this possibility if feticide is not carried out prior to delivery late in pregnancy. The spectrum of responses to a live-born fetus following a termination procedure ranges from full neonatal intensive care (NICU) unit resuscitation efforts to euthanization.[34] Protocols for feticide, typically by intracardiac injection of potassium chloride, have been proposed by individuals and professional organizations for any planned TOPFA after 22 weeks' gestational age to avoid the possibility of a live birth.[79]

Improved early detection and increased access to screening may decrease the rates of late TOPFA, but the moral debate will likely continue. Medical advances in fetal imaging and improved premature infant survival

have blurred the line between fetus and newborn. This phenomenon has simultaneously "fetalized" newborns, on the one hand, and personalized fetuses, on the other, and has been used as justification for both the euthanization of newborns, if they are not that different from fetuses, and increased restrictions on pregnancy terminations.[83] The gravity and complexity of these issues must be appreciated by the urologist whenever conducting prenatal counseling in which the termination of a pregnancy may be an option.

OBSTRUCTIVE UROPATHY WITH OLIGOHYDRAMNIOS

According to the Society for Fetal Urology consensus statement from 2010, prenatal hydronephrosis may be detected in up to 5% of pregnancies.[84] However, most cases are mild with a low incidence of true urologic pathology, and only 1 in 30,000 pregnancies is estimated to be a potential candidate for prenatal intervention because of an obstructive lesion.[5,68,85–88] Urethral atresia is the most common cause of early severe hydroureteronephrosis. Posterior urethral valves (PUVs) (Figure 6.2) may present either early or late in the pregnancy with varying degrees of renal injury. A ureterocele obstructing the bladder neck due to a ball valve mechanism is another rare form of bladder neck obstruction more common in females.[89] Obstruction from any of these lesions causing oligohydramnios remains rare, and pediatric urologists continue to have a role in preventing unnecessary prenatal intervention.

The negative impact of early severe obstruction on lung development has been well documented.[90–94] After early animal studies showed promise for prenatal intervention to improve the deleterious effects of LUTO on renal and pulmonary development,[90,95,96] numerous trials of vesicoamniotic shunts (VASs) (Figure 6.3) on human fetuses have been performed since the early 1980s.[56] Unfortunately, outcomes after intervention in humans have been more mixed.

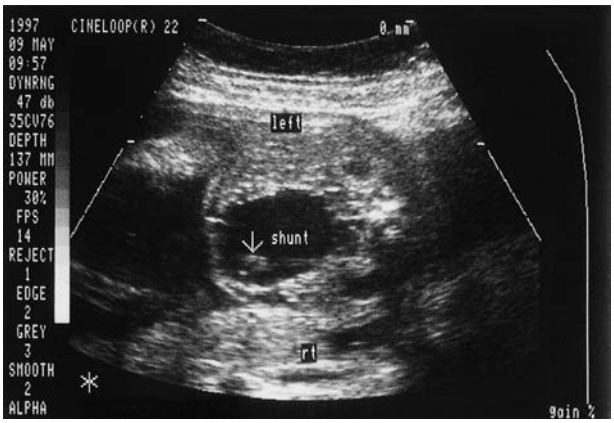
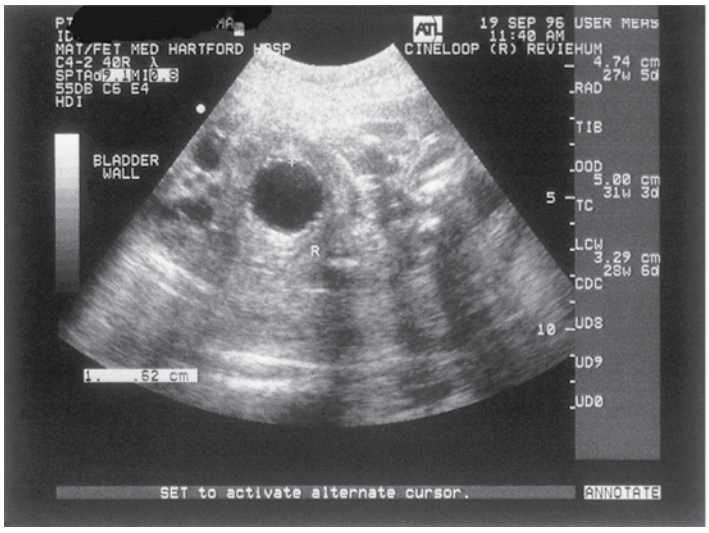


FIGURE 6.3 Antenatally detected PUVs with percutaneously placed VAS.

Limited data from early studies of prenatal intervention for human fetal uropathies supported the efficacy of intervention,[88,97–102] but data were limited in size and quality. Published reports concerning the results of intervention are mostly retrospective in nature without long-term follow-up.[56,103] In addition, the natural history of these lesions differs in the timing of presentation and their severity, even during the prenatal period, making case comparisons difficult.[56,104]

The largest systematic review to date on outcomes after prenatal intervention for LUTO showed improved perinatal survival with intervention (odds ratio [OR] 3.82%, 95% confidence interval [CI] 2.14–6.82), with the largest effect seen in the group with the poorest pretreatment prognosis. Only those with the best pretreatment prognosis appear to show improved survival with normal renal function, but this was not statistically significant (OR 2.98%, 95% CI 0.45–19.62). When all prognostic groups were included, there was actually a trend favoring no treatment, again not statistically significant (OR 0.67%, 95% CI 0.22–2.00).[56] Simple diversion does not

(a)



(b)

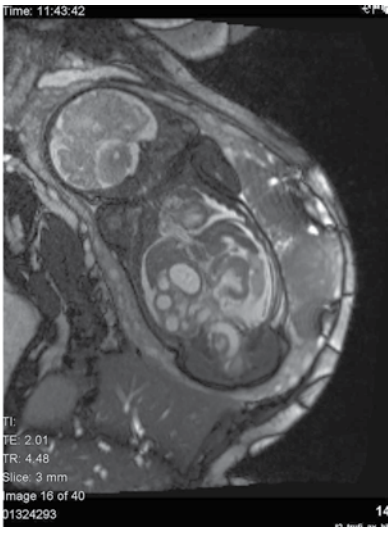


FIGURE 6.2 Prenatal PUVs: (a) prenatal sonogram and (b) fetal MRI showing bilateral dilated renal pelvises and bladder with oligohydramnios. (Image courtesy of Dr. R. Nicholas Trane.)

appear to be adequate to completely prevent or reverse the effects of LUTO.

VAS also carries a significant rate of complications, such as shunt migration (34%), preterm premature rupture of membranes, chorioamnionitis, and fetal death.[56] Fetal cystoscopy with valve ablation has been performed since the mid-1990s in an attempt to establish more natural bladder cycling, provide a more accurate diagnosis, and avoid complications, such as shunt migration. To date, no significant benefit has been shown over VAS, but numbers are small and no randomized controlled trials have been performed.[65]

Selection criteria to consider that will maximize the potential benefit to treatment generally include (1) karyotype excluding chromosomal abnormalities and demonstrating male sex; (2) exclusion of other significant structural abnormalities that may negatively impact prognosis; (3) oligohydramnios or anhydramnios; (4) singleton pregnancy; (5) sonographic evidence of obstruction, such as bilateral hydronephrosis, megacystis, or renal changes; and (6) evidence of recoverable renal function.[105] Female fetuses are typically excluded because obstruction usually accompanies more complicated developmental abnormalities and intervention has not been shown to improve outcomes in those cases. Serial sampling of fetal urine by repeat vesicocentesis should be used to assess renal function, but carries the obvious risks to the fetus and mother (see section on Complications of Prenatal Intervention). Various predictors of renal function are presented in Table 6.2. Sodium and calcium appear to be the most accurate at predicting poor renal function,[106] but precision is still lacking. Fetuses with the best prognosis have the strongest indications for intervention.

Fetuses otherwise meeting inclusion criteria, but with borderline urine analyte levels, may benefit from intervention that may reduce the risk of fatal pulmonary hypoplasia, but early dialysis and renal transplant may still be required.[105] Other situations may be considered for prenatal intervention on an individual basis, such as obstruction of a solitary kidney,[107] although these situations are incredibly rare.

A single-center review of 18 patients with a mean follow-up of 5.8 years revealed that 6 patients (33%) required renal transplantation, 4 (22%) had renal insufficiency, and 8 (45%) had normal renal function.[88] Three patients (16.5%) required catheterization as an adjunct to voiding, and three more as the sole means of bladder emptying. Pulmonary and musculoskeletal issues persisted in 45% and 50%, respectively. Quality of life measures were not statistically different compared with a healthy population, but numbers were small and CIs were wide.

A multicenter registry was attempted in the past, but only a small number of patients were entered and long-term follow-up was not obtained.[108] Ultimately, multicenter endeavors, such as the North American Fetal Therapy Network (NAFTNet), will be required to answer many of the unanswered questions concerning appropriateness of intervention. A survey of practicing pediatric urologists confirmed that few recommend prenatal intervention. When it is considered, the strict criteria outlined above should be followed.[109] Ideally, intervention should occur before any renal injury occurs. This approach will only happen if future studies can accurately identify obstruction very early in the prenatal period, which is currently rarely accomplished.

Postnatal Evaluation and Management of PUV and Ureterovesical Anomalies

The cause of LUTO is now commonly diagnosed presumptively in the antenatal period. Previously, infants presented with failure to thrive, an abdominal mass, or urosepsis.[110] Common antenatal ultrasound findings include a distended thick-walled bladder, bilateral hydronephrosis, and oligohydramnios in some cases.[110–112] Fetal MRI can provide increased anatomic detail and possibly prognostic information, such as the quality of renal parenchyma.[12–16,113] Normal prenatal imaging and wet diapers do not exclude the possibility of LUTO in the neonatal period,[114] and suspicion should remain high when clinical signs, such as distended abdomen or urinary tract infection (UTI), are present. Normal voiding cystourethrogram also does not exclude the presence of valves, as 30% of patients with valves have normal findings.[115] While the outcomes of patients diagnosed earlier may be worse than those diagnosed later, this is indicative of a greater severity of disease and should not be taken to mean that antenatal diagnoses will not improve outcome in these patients.[116,117]

There is significant variability in the treatment of infants with PUV. Appropriate treatment is usually determined based on the overall medical condition of the infant, including renal function, hydrational status, presence of infection and lung maturity, and caliber of the urethra.

TABLE 6.2 Fetal urine electrolytes predicting renal function based on final of three or four serial bladder aspirates

	Good prognosis	Poor prognosis
Sodium	<90 mmol/L	>100 mmol/L
Chloride	<80 mmol/L	>90 mmol/L
Osmolality	<180 mOsm/L	>200 mOsm/L
Calcium	<7 mg/dL	>8 mg/dL
Total protein	<20 mg/dL	>40 mg/dL
β_2-Microglobulin	<6 mg/L	>10 mg/L

Source: Wu S, Johnson MP. *Clin Perinatol* 2009;36(2):377–90.

In general, some basic tenets are applicable to most cases. Catheter drainage of the bladder will allow decompression of the urinary tract, and prophylactic antibiotics should be initiated at birth. Circumcision may reduce the risk of breakthrough UTIs when reflux is present.[109,118] Initial measures of renal function are reflective of the mother's kidney function; therefore, catheter drainage should be maintained until the nadir creatinine is reached.[119–123] If the creatinine falls below 1 mg/dL, valve ablation with pediatric endoscopic equipment should be performed, after which careful monitoring of renal function, bladder function, and reflux should be continued while the child remains on antibiotic prophylaxis.[123–125] Early use of anticholinergics in children with increased voiding pressures and reduced bladder capacity may improve bladder function after primary ablation.[126]

Infants whose renal function does not substantially improve pose a much more difficult management problem. In these patients, minimizing intrarenal pressure may have a positive effect on renal function. These patients may have either low or high urinary diversion.[119,120,123,127,128] While upper tract diversion was commonly used in the past, vesicostomy is usually the initial step to decompress these kidneys. Primary vesicostomy and upper tract diversion do not appear to have an adverse effect on bladder function compared with primary ablation.[129,130] Consideration of upper tract diversion may be given in severe cases in order to minimize intrapelvic pressures and in those with urinary infection, as this optimizes renal drainage. However, little evidence exists that upper tract diversion really helps, unless infection has been present, and it complicates subsequent reconstruction. The long-term outcome in these patients depends essentially on the degree of renal damage and on bladder function.[116,131] Older children may require anticholinergics and/or bladder augmentation for the "valve bladder" if high storage pressures are demonstrated on urodynamics. Reimplantation to correct reflux may be necessary. Renal insufficiency and end-stage renal disease requiring dialysis or transplant develop in approximately 35% and 15%, respectively, with a nadir creatinine of less than 1 mg/dL having the most predictive value for adequate renal function.[132] Data are limited, but recent research on long-term sexual function of patients with PUV shows rates of erectile and ejaculatory disturbances and infertility similar to those of the general population; however, rates may be higher in patients with cryptorchidism or uremia.[133,134]

An ectopic ureterocele can present as an obstructing lesion at the bladder neck. This condition occurs with a female prevalence of approximately 3–4:1.[80,136,137] Prenatal ultrasound has detected cases in which the ureterocele creates a ball valve obstructive and cases of bilateral ureteroceles.[80] Prenatal and postnatal MRI have been used increasingly in the diagnosis of ureteroceles if ultrasound is inconclusive.[138,139] In general, these patients are managed initially by transurethral incision or puncture (Figure 6.30).[140–146] Puncture techniques have been gaining popularity after many reports of reduced rates of iatrogenic vesicoureteral reflux (VUR) compared with incision,[145,146] but numbers are still small to make definitive conclusions. Once stabilized, they undergo final management, which may include treatment of reflux, excision of the ureterocele, and in some cases, upper-pole nephrectomy and ureterectomy.[136] In general, the recent trend has been toward less aggressive management of ureteroceles and associated abnormalities.[147] Many cases of nonobstructed ureteroceles or those associated with nonfunctioning renal units have been managed nonoperatively with good results.[148,149] Associated VUR has also been shown to resolve in many instances. Infection is another indication for ureterocele incision or puncture. As in all cases of LUTO, treatment of long-term bladder dysfunction may be required.

VUR can be the cause of the upper tract dilation in as many as 35% of children with antenatal hydronephrosis.[109] Recent reviews suggest that this is less likely in African Americans and more common in males than females,[150,151] but all should be screened. Children with dilated upper tracts should have a voiding cystourethrography (VCUG) to rule out reflux prior to treatment for other urinary tract abnormalities.[152] The recent American Urologic Association (AUA) guidelines on VUR highlight the need to evaluate and treat associated bowel and bladder dysfunction (BBD) when feasible, preferentially before surgical intervention for VUR. Continuous antibiotic prophylaxis (CAP) is indicated for children less than 1 year in age with a history of febrile UTI, or high-grade (III–V) reflux, and optional for those with lower grades of reflux without febrile UTIs. Circumcision should be offered as an option to any male neonate with VUR, as it may decrease risk from UTIs.[153]

NEURAL TUBE DEFECTS

Although not primarily a urologic abnormality, neural tube defects, including open defects (meningomyelocele) and closed defects (lipomeningocele and sacral agenesis), result in significant urinary tract morbidity. The timing of neurosurgical repair differs for each based on the likelihood of complications as follows: meningomyelocele, prenatally and immediately postnatal; lipomeningocele, within the first year; and sacral agenesis, as symptoms dictate.

The use of folic acid supplementation and the termination of affected fetuses led to a significant decrease in the birth rate of children with myelomeningocele, which has since stabilized at 3.4 per 10,000 live births.[62,154–158] The Public Health Service of the United States currently recommends that all women capable of childbearing consume 0.4 mg of folic acid per day and pregnant women consume 0.6 mg per day to decrease the risk of neural tube defects and anencephaly.[159] There is a slight increase in the incidence of myelodysplasia if other family members also have the condition.[160,161]

Meningomyelocele

The accurate diagnosis of open neural tube defects during the prenatal period is achievable in nearly all cases by a combination of routine screening of maternal serum α-fetoprotein and targeted sonography.[162,163] For prognostic purposes, prenatal ultrasound is able to predict the level of the spinal cord lesion within one and two levels in 78% and 96% of cases, respectively, for open spinal cord

defects with improved accuracy and tertiary centers.[52] Neuropathic bladder effects have been detected before birth.[164,165]

There is evidence of progressive neurologic deterioration during gestation, likely from continued exposure of the spinal cord to amniotic fluid and trauma during birth.[166–169] These findings, combined with promising early results from animal and human studies on prenatal intervention, led to a large-scale randomized controlled trial of prenatal versus postnatal intervention.

The Management of Myelomeningocele Study (MOMS) halted accrual early at 183 of the planned 200 patients due to early demonstration of efficacy.[170] Prenatal intervention showed reduced rates of infants meeting criteria for ventriculoperitoneal shunt placement (65% vs. 92%) and reduced hindbrain herniation. Overall functional outcome scores were also significantly higher in the prenatal intervention group. The prenatal group also had a significantly higher rate of preterm birth, intraoperative complications, uterine scar defects, and maternal transfusion. Those receiving prenatal intervention also had a higher rate of subsequent surgery for a tethered cord (8% vs. 1%). Prenatal myelomeningocele repair will likely soon be routinely offered at fetal centers around the United States.[171]

High-quality data from MOMS on bladder function is currently unavailable, but short-term follow-up and retrospective data from earlier studies have not shown any urologic benefit to prenatal intervention compared with postnatal intervention. The durability of prenatal intervention is also still unknown. The urologic care of these patients does not significantly differ from those treated in the postnatal period[172] and requires close follow-up based on urodynamic studies.

Open myelomeningoceles (Figure 6.25) are readily identifiable at birth. The level of the lesion does not correlate with the neurologic defect because some nerve roots may be left intact. An Arnold–Chiari malformation can affect the brainstem and pontine micturition center. It is this malformation that is most likely to be prevented by fetal surgery. Tethering of the spinal cord and different growth rates in the distorted vertebral bodies can affect the final neurologic deficit.[173] Likewise, immediately after birth and during infancy and early childhood, a changing pattern is often seen in the urodynamics of these patients.[174–176] It is impossible to make broad generalizations, but in children with high thoracic lesions, patients may have an intact sacral reflex arc. Those with lesions at S1 and below can have normal bladder function, but upper or lower motor lesions involving the bladder and/or pelvic floor are also seen.

Surgical closure of the spinal defect does not equal a cure from urologic sequelae. Comparison of postvoid residuals actually found higher values in the immediate postsurgical period, likely from spinal shock.[177] Although a less invasive approach is favored by some in hopes of avoiding unnecessary catheterization and urodynamic testing, a proactive approach, including early initiation of clean intermittent catheterization (CIC), prophylactic antibiotics in any child with hydronephrosis, and full urologic workup, including renal sonography, VCUG, and urodynamics, yields important prognostic information and has been shown to protect both upper and lower tract systems.[174,178–186]

Initial management usually involves initiation of CIC every 4–6 hours in all children that is continued after surgery. Frequency may be reduced if postvoid residuals decrease or CIC stopped all together if no urine is found when catheterizing, but it is important for all parents to learn CIC during the initial hospitalization to be used if needed. Prophylactic antibiotics are started in any child with evidence of reflux. Circumcision may be considered for male patients, as it has been shown to decrease the risk of UTIs in patients with reflux.[109] Use of the Credé maneuver should be avoided. Urodynamics are typically performed after surgical spinal closure by around age 6 weeks, and anticholinergic medication is started if excessive uninhibited bladder contractions are present. The dynamic nature of this disease requires routine surveillance throughout the patient's life, but particularly during periods of rapid linear growth, when spinal cord tethering may occur.[184,187]

Lipomeningocele

This abnormality is difficult to identify on physical examination, but the vast majority of children with lipomeningocele have an identifiable superficial or cutaneous lesion. A high level of suspicion and careful examination of the lower spine will help detect the disease early, which is particularly important, as recent research suggests that those surgically repaired by 1 year of age have better long-term urologic outcomes than those repaired later.[188] Prenatal detection, although exceedingly rare,[189] would allow earlier intervention and likely improve outcomes.

The neurologic changes occur because of an intradural lipoma. This lesion results in a broad spectrum of disease and presentation.[190] Typically, during early childhood, there are few outward physical abnormalities, and only with complete urodynamic assessment is the effect on the bladder identified.[191] The most common urodynamic findings are consistent with an upper motor neuron lesion. Sphincter dyssynergy is less often identified in this group. In older children where the diagnosis has been delayed, there are often neurologic changes in the lower extremities.[192] The bladder changes in the older group are mixed between detrusor hyperreflexia and detrusor areflexia. The best methods to identify and characterize these lesions are MRI and complete urodynamic assessment.[193]

Sacral Agenesis

This lesion is even more difficult to identify on physical examination, and often the patient presents at an older age with failure to become continent.[194–196] Loss of the lower vertebral bodies can be easily seen on a lateral lower plain film of the spine or on MRI. White and Klauber suggested that palpation of the coccyx could identify absent vertebral bodies, but radiographic confirmation is the best method.[197] These patients have a stable neurologic lesion that does not progress with growth. However, the results of urodynamic studies are variable.[196,198] Patients may have no sign of denervation or hyperreflexia, areflexia, intact sphincter function, or sphincter dyssynergy, and

some have absent control over the sphincter.[199] A high level of suspicion and complete urodynamics help to guide treatment, with specific intervention based on the identified findings.[194–196]

DISORDERS OF SEX DIFFERENTIATION

The identification of disorders of sex differentiation (DSDs), formerly referred to as intersex disorders, in the prenatal period is the result of better screening techniques and advances in the understanding of the inheritance of these diseases. Unlike the postnatal period, where the discovery of ambiguous genitalia is the initiating factor, amniocentesis, CVS, and improved sonographic techniques allow prenatal identification of many cases of DSDs.[200–205] The prenatal identification of these problems results in the need to provide adequate prenatal counseling.[206,207] Regardless of the timing of identification, complex medical, social, and psychological aspects of a new diagnosis of DSD, although medically speaking not an emergency, do need to be handled with sensitivity and immediacy to optimize long-term outcomes. A multidisciplinary approach by an experienced team, including a pediatric urologist, endocrinologist, geneticist, and psychiatrist or psychologist, is best. In most instances, sexual assignment is straightforward, and where it is not, consideration should be given to delaying the decision to intervene surgically until the infant is older[208,209] (see Chapter 29). The nomenclature for DSDs underwent a substantial revision in 2005.[210] A large panel made up of medical and lay experts devised a new system that classified DSDs based on chromosomal genotype and physical attributes. Terms assigning a specific gender or carrying any negative connotations were avoided. Specifically, terms such as *intersex*, *male*, *female*, *hermaphrodite*, or *pseudohermaphrodite* were replaced with conditions such as 46,XX DSD, 46,XY DSD, and sex chromosome DSD.

CAH, in particular, has been a model for prenatal pharmacotherapy. Identifying CAH before birth provides the opportunity to treat the fetus in the hope of preventing androgen effects on fetal development, although therapy is still most effective based on known familial risk rather than a confirmed diagnosis.[211–219] CAH is the most common cause of ambiguous genitalia at birth and of 46,XX DSD. It is the only form of DSDs that can be life threatening.

The worldwide incidence of CAH is estimated at 1 in 15,000 live births, with significant ethnic variation.[220] Classic CAH, a deficiency of the 21-hydroxylase (21-OH) enzyme, accounts for 95% of cases of CAH and is the most severe form.[217] Other enzyme deficiencies and associated genes are shown in Table 6.3. The 21-OH enzyme is part of the cytochrome p450 enzyme family and is encoded by the *CYP21A2* gene located on the short arm of chromosome 6.[214] Deficiency of 21-OH results in the inability to synthesize cortisol. The pituitary and hypothalamus overstimulate the adrenal gland, causing the overproduction of androstenedione. The androstenedione is further metabolized, predominantly to testosterone and dihydrotestosterone (DHT), resulting in the prenatal virilization of the female fetus. A variety of identified deletions and point mutations of the *CYP21A2* gene lead to a spectrum of severity in classic CAH, with 75% experiencing the congenital salt-wasting (SW) form of the disease and the remaining 25% with the simple virilizing (SV) form.[171,215,217] Both SW and SV forms are associated with a range of external genital virilization. It is this virilization that is the target of prenatal therapy (Figure 6.29).

TABLE 6.3 Possible enzyme deficiencies and associated genes in CAH

21-Hydroxalase	*CYP21*
11β-Hydroxalase	*CYP11*
18-Hydroxylase	*CYP11*
18-Oxidase	*CYP11*
17,20-lyase	*CYP17*
17α-Hydroxylase	*CYP17*
3β-Hydroxysteroid dehydrogenase	*3β2HSD*
Side-chain cleavage enzyme	*StAR*

Early treatment with dexamethasone can prevent or minimize severe genital abnormalities in some patients.[214,218,221–223] A recent meta-analysis demonstrated an overall reduction in virilization measured by a Prader score of –2.3 (95% CI –3.4 to –1.3) for fetuses treated with maternal dexamethosone,[218] although the overall data quality was low, based mainly on observational studies. Despite the known beneficial effect of prenatal treatment of affected female fetuses with CAH, there is continued controversy, which exemplifies that of many prenatal treatments.[224–227]

The current controversy is in large part due to the time disparity between the accurate diagnosis of CAH and the ideal initiation of therapy. Adrenal steroidogenesis begins in the fetus during gestation weeks 6–7, and external genital differentiation takes place during weeks 7–12. Prenatal treatment of CAH should start before week 6 or 7 to completely prevent androgenic effects; however, a diagnosis of CAH depends on invasive CVS to obtain fetal DNA that cannot be done until 9–12 weeks' gestation. Treatment (20 μg/kg/day of oral dexamethasone divided into three daily doses) is therefore begun as soon as pregnancy is confirmed in all at-risk fetuses, which are defined by a diagnosis of CAH in an earlier pregnancy. Since CAH is inherited in an autosomal recessive manner, the risk of having a female infant with classic CAH for any pregnancy by two parents with a previously affected child is one in eight. Males do not need to be treated since excess androgens do not harm their fetal development. This means that seven fetuses are treated unnecessarily for every one female with CAH that benefits from treatment.

Newer noninvasive methods to differentiate fetal sex based on detection of cell-free fetal DNA (cffDNA) in maternal serum have been able to identify male fetuses as early as 7 weeks' gestation and accurately determine fetal sex as early as 8 weeks.[228] This technology has yet to reach clinical practice.

Maternal dexamethasone has been shown to be overall well tolerated, although edema, striae, and weight gain are more prevalent, while there is insufficient evidence of serious complications, including hypertension and gestational

diabetes.[218,229] Long-term effects to the children born to mothers receiving dexamethasone are incompletely understood, but there is some concern for increased incidence of social anxiety or difficulty with specific learning skills.[219] The fetal metabolism of dexamethasone is not understood, and the doses recommended for treatment are greater than required to suppress the adrenal in the adult.[224]

These concerns are apparent in the clinical guideline on CAH published by the Endocrine Society in 2009. The clinical guideline on CAH recommends that prenatal treatment of CAH be considered experimental and conducted as part of institutional review board investigations when possible.[227] No specific protocols were issued. The promise for future widespread clinical application lies in more robust prospective data on all aspects of prenatal steroid therapy, combined with the ability to predict who will benefit from treatment as early as possible.

Most cases of DSDs other than CAH are identified inadvertently.[204,230] In some cases, this is the result of an amniocentesis because of a simple parental request to know the sex of the fetus. In other cases, there can be an issue of other known inheritable diseases, such as determining the likelihood of an X-linked disorder (e.g., hemophilia). Knowing the sex may be helpful in confirming the cause of a structural disorder (e.g., PUV) that does not occur in girls. In cases with a family history of CAH, genetic sampling can identify the inherited genetic disorder. The identification of DSD may also result from routine screening of an older mother. In situations where the genetic sex is known, but the genital screening by ultrasound does not appear to match the genotype, clinicians should consider the possibility of DSD. In the case of a 46,XY karyotype with female-appearing genitalia, the differential diagnosis should include gonadal dysgenesis or androgen insensitivity. In severely androgenized females with CAH, a 46,XX karyotype may be associated with ultrasound findings suggesting male genitalia. Table 6.4 lists the chromosomal analyses and possible DSDs.

Postnatal Evaluation of Disorders of Sex Differentiation

The postnatal consultation for ambiguous genitalia is one of the urgent problems that a urologist must face. The initial approach to managing DSD patients is to identify and treat possible life-threatening abnormalities.[208,231,232] Although CAH is the most common form of DSDs resulting in ambiguous genitalia at birth, it is important to have a diagnostic plan for evaluating all patients. A practical algorithm using the new DSD terminology based on history, chromosome determination, serum tests, screening radiological studies, and pathology was published by Lambert et al.[30] and is used by the authors (Figure 6.4).

TABLE 6.4 Chromosomal analyses and possible disorder of sexual development

46,XX	CAH Maternal virilizing syndrome Ovotesticular DSD Gonadal dysgenesis
46,XY	5α-Reductase deficiency Androgen insensitivity syndrome Dysgenetic testes Primary testicular failure Leydig cell failure Persistent Müllerian duct syndrome
46,XX/XY	Ovotesticular DSD
45,X, 45,X/46,XX, 45,X/46,XY, etc.	Ovotesticular DSD Gonadal dysgenesis (pure or partial)

The initial history should focus on degree of prematurity, family history (urologic abnormalities, perinatal deaths, precocious puberty, amenorrhea, etc.), and drug ingestion history (oral contraception during pregnancy or hormones for assisted reproductive techniques). One may note virilization or a cushingoid appearance of the mother, and review of prenatal tests, such as sonography or karyotype, may be helpful.

Physical examination and screening laboratory studies facilitate the differential diagnosis relatively rapidly. Female infants with CAH will have varying degrees of virilization, from hypertrophy of the clitoris and mild labioscrotal development to a normal-appearing male phallus and scrotum. Palpation of the gonads suggests a differential diagnosis. If no gonads can be palpated with ambiguous or masculinized genitalia, all forms of DSDs are possible, with 46,XX being the most common. When only one gonad is palpable, one should consider 45,X/46,XY DSD, ovotesticular DSD, and 46,XY DSD. When both gonads are palpated, 46,XY DSD and rarely ovotesticular DSD are typically diagnosed.

The next step involves targeted laboratory and radiologic screening. Initial evaluation should include measuring serum electrolyte, 17-hydroxyprogesterone, testosterone, DHT, follicle-stimulating hormone (FSH), and luteinizing hormone (LH). Radiologic evaluation consists of pelvic sonography and VCUG. When 17-hydroxyprogesterone is elevated, the karyotype is 46,XX, and a uterus is identified by ultrasound, one is dealing with CAH. Checking the 11-deoxycortisol levels can differentiate between 21α-hydroxylase and 11β-hydroxylase deficiency. If 11-deoxycortisol levels are low, then 21α-hydroxylase deficiency is confirmed, where as 11β-hydroxylase deficiency will show elevated 11-deoxycortisol.

If the 17-hydroxyprogesterone levels are normal and a uterus and ovaries are identified in a child with a 46,XX karyotype, a maternal virilizing syndrome should be considered the cause of the 46,XX DSD.

A combination of imaging findings and laparoscopy with or without biopsy is often required to make a definitive diagnosis in patients without CAH as the cause of the ambiguous genitalia. Sonography is only 50% accurate in locating abdominal testicles,[233] but it can typically identify inguinal testicles and assess Müllerian structures. If ultrasound proves inadequate, MRI or a fluoroscopic genitogram may provide additional valuable information. Open or laparoscopic exploration with biopsy is required when testes are nonpalpable or intra-abdominal. When biopsy identifies a streak gonad, one should consider gonadal dysgenesis, which is pure when both gonads are represented as streaks (45,X, 45,X/46,XX, 46,XX, and 45,X/46,XY) or partial when one streak gonad and one testis are present (45,X/46,XY and 46,XY). In cases with both a testis

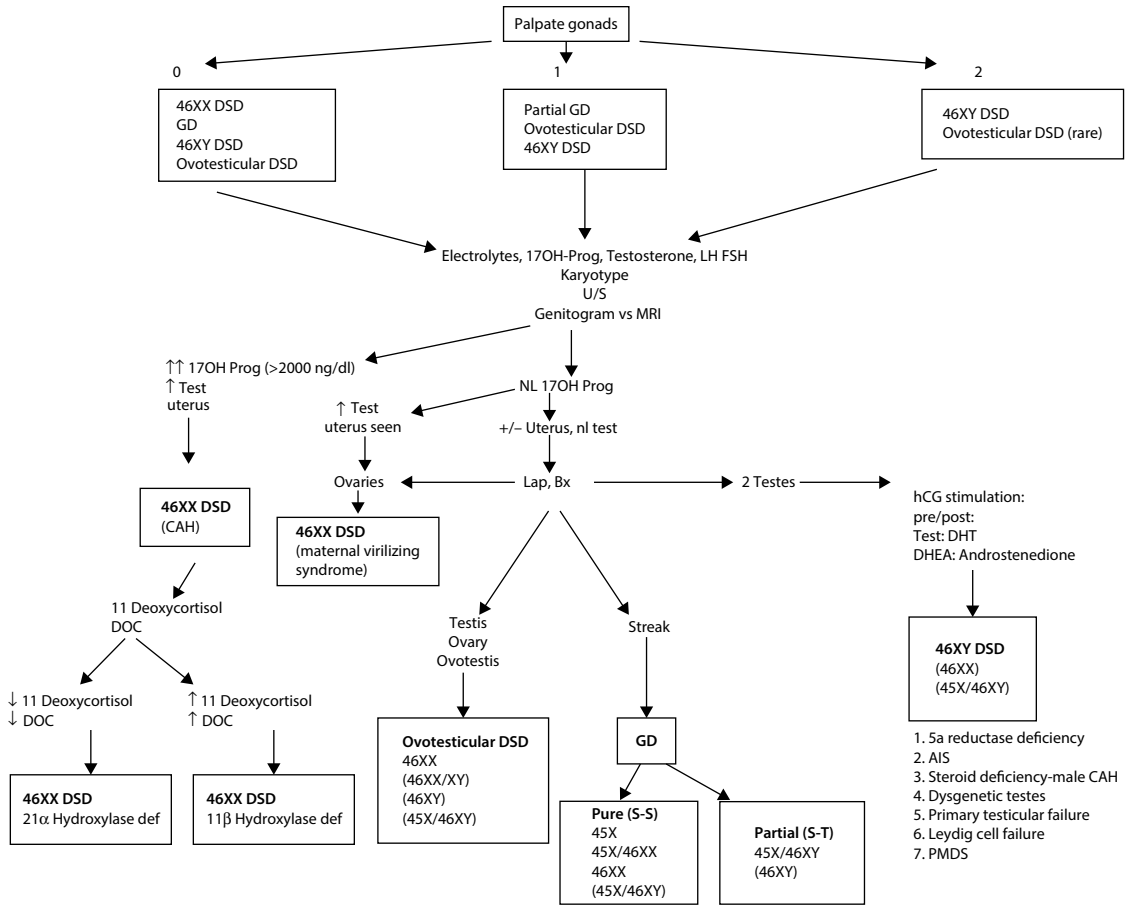


FIGURE 6.4 Anatomic and endocrine approach to DSD evaluation. NL, normal; S, streak gonad; T, testis. (Adapted from Lambert SM et al. *Urol Clin North Am* 2010;37(2):195–205.)

and ovary or two ovotestes, one should consider ovotesticular DSD (46,XX, 46,XX/XY, and 46,XY). If two testes are identified, an hCG stimulation test should be performed. Serum testosterone, DHT, dehydroepiandrosterone (DHEA), and androstenedione should be measured before and after stimulation. This will identify the cause of the 46,XY DSD. A testosterone-to-DHT ratio of greater than 20 suggests 5-α-reductase deficiency. Other causes of 46,XY DSD include testicular failure, dysgenetic testes, steroid deficiency secondary to male CAH, persistant Müllerian duct syndrome, complete androgen insensitivity syndrome, and exogenous influences.

Karyotyping should be performed even if prenatal chromosomal studies from amniocentesis have been done. In cases of CAH, the Barr body is positive. Urinalysis should be performed. Screening sonography and genitography in appropriate situations are helpful in the evaluation, in order to identify ovaries and a uterus.

Initial treatment involves glucocorticoid and mineralocorticoid replacement. It is strongly recommended that these patients be reared as female because of the chromosomal sex and potential fertility, but in the most virilized form, questions have arisen as to the best sex of rearing.[209,234,235]

Initial genetic testing includes metaphasic karyotyping of chromosomes. Interphasic fluorescent in situ hybridization (FISH) can be used for more detailed analysis of the sex chromosomes or mosaicism. Genes associated with many causes of DSDs, such as CAH and complete androgen insensitivity, are now known and can be sequenced to determine a patient's specific mutation. Genetic sequencing is best carried out at a later date when history, physical exam, and preliminary tests have narrowed the diagnosis. Input from genetic counselors is essential so that parents understand the implications for themselves, the patient, and current and future siblings.

ABDOMINAL MASSES

The prenatal identification of a solid mass seldom requires early intervention but often generates an urgent consultation. The neonate presenting with an abdominal mass is of particular importance to the pediatric urologist because the majority of such lesions arise in the retroperitoneum in general and the kidney specifically.[236–239] Traditionally, they presented with a palpable mass. Although some still present this way, masses are far more likely to be detected by prenatal sonography. At the time of presentation to the urologist, most have already been categorized as solid, cystic, or hydronephrotic. The urologist must be familiar with

the masses that originate from the genitourinary tract, as well as the following broad spectrum of other potential etiologies:

1. Hydronephrosis and renal cysts
   a. Nonobstructive hydronephrosis
   b. Ureteropelvic junction (UPJ) obstruction
   c. Unilateral cysts (multicystic dysplastic kidney [MCDK] and multilocular cystic nephroma)
   d. Bilateral cysts (autosomal recessive and autosomal dominant polycystic kidney disease [ADPKD])
2. Midline cystic abdominal masses
   a. Hydrometrocolpos
   b. Ovarian cyst
   c. Distended bladder
   d. Urinary ascites
3. Solid abdominal masses
   a. Neuroblastoma
   b. Sacrococcygeal teratoma
   c. Congenital mesoblastic nephroma
   d. Wilms' tumor, rhabdoid tumor, clear cell sarcoma, angiomyolipoma, and ossifying tumor of the kidney
   e. Renal vein thrombosis (RVT)
   f. Renal artery thrombosis
   g. Adrenal hemorrhage
   h. Rhabdomyosarcoma
   i. Germ cell tumor

Figure 7.16 provides a flow diagram that outlines the general framework used to evaluate the lesions identified antenatally. The evaluation of an infant with a mass often becomes a continuation of the evaluation that began prenatally. Ultrasound, plain films, computed tomography (CT) scans, and MRI all have important roles in the imaging of pediatric abdominal masses.[238,240,241] It is important to note that neonates with masses represent a diagnostic emergency for both the parent and the referring physician, but rarely do they require emergency surgery, and prenatal intervention is almost never indicated.

Hydronephrosis and Renal Cystic Lesions

UPJ obstruction causing hydronephrosis remains one of the most common causes of an abdominal mass in the neonate.[242,243] The diagnosis is almost always made by prenatal ultrasound.[238,244] Significant hydronephrosis has an incidence of approximately 1:600 infants; however, hydronephrosis causing an abdominal mass is much less common.[245] Barring the development of oligodramnios or anhydramnios, most fetuses are observed until term delivery. UPJ obstruction is usually unilateral but can be bilateral in up to 20%–40% of cases.[246,247]

Postnatal management includes prophylactic antibiotics and postnatal sonography. Waiting 48 hours after birth to perform ultrasound examination is often recommended to minimize the incidence of false-negative studies,[248] although the data suggest that this traditional delay is unnecessary.[249] Clearly in the face of a neonate with a mass, no delay is warranted. If hydronephrosis is detected and no ureter is visualized, the presumed diagnosis of UPJ is made. A VCUG will exclude the possibility of ipsilateral or contralateral reflux. This test should be performed before any intervention is considered. To establish the diagnosis, a well-tempered renogram is performed. When performing lasix renograms, it is important to optimize the study by following an accepted protocol and ensuring that the infant is well hydrated.[250–252] Prophylactic antibiotics are discontinued when reflux and obstruction are excluded.

In cases where it is believed that the obstructed kidney may have minimal function, proceeding with evaluation and treatment earlier is often indicated because the neonatal kidney has significant ability to regain function.[253] When presentation involves an abdominal mass from massive hydronephrosis, evaluation of the viable renal parenchyma is difficult. In these cases, a period of percutaneous drainage, followed by nuclear scintigraphy to evaluate function, may reveal a salvageable renal unit. A biopsy at the time of surgical correction has the best predictive value with regard to future renal function (Figure 6.5).[254] If no function is present on the renal scan, the diagnosis of MCDK must be considered.

Surgical treatment of UPJ obstruction will be required in approximately 20% of the cases and depends on the degree of obstruction and whether the lesion is unilateral or bilateral.[248,255] Clearly, children with significant bilateral obstruction require early intervention. Since surgical repair of UPJ in infants does not have a higher complication rate than in larger children, age does not affect the decision to intervene surgically.[256]

Increasingly, cystic renal lesions in the neonatal period are detected antenatally by sonography. In evaluating these lesions, it is useful to divide them into unilateral and bilateral categories. This allows a natural division of diagnostic possibilities.[257] Most lesions are detected antenatally but do not require intervention or further evaluation until after birth.

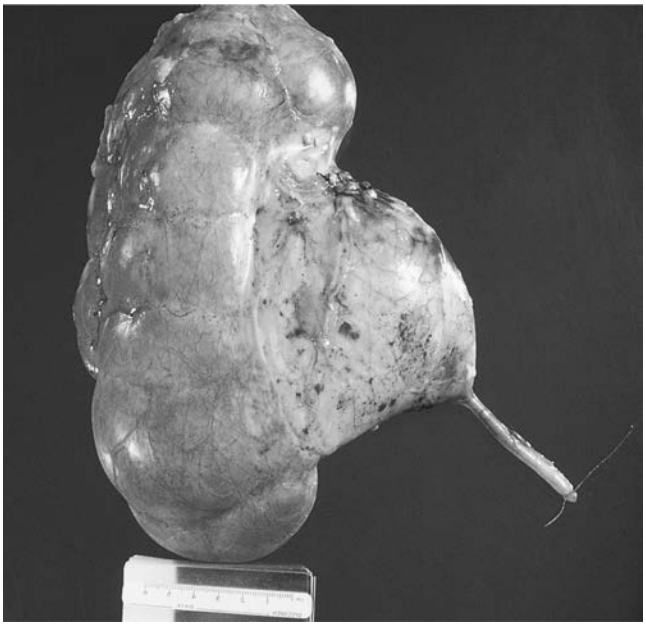


FIGURE 6.5 End-stage UPJ obstruction showing how the dilated calyces can mimic cystic structures.

Unilateral Cystic Lesions

With an overall incidence of 1 in 4300, MCDK is the second most common cause of an abdominal mass in infants.[258,259] Usually, the mass is unilateral and may be palpable as a multilobular "cluster of grapes" that transilluminates. These lesions may be quite large and can impede normal feeding because of compression of the stomach; alternatively, they may impinge on the diaphragm and affect respiration. Importantly, this lesion has a high incidence of associated contralateral renal abnormalities. Contralateral lesions are seen in 25%–31% of these children.[259–261] The two most common kidney lesions are UPJ obstruction and contralateral VUR. Miller et al. recently reported an incidence of contralateral VUR of 26.4%. The majority (89%) of the VUR was low grade (I or II). The majority of the cases underwent spontaneous resolution.[262] While ultrasound evaluation of the contralateral kidney should be performed, the need for a VCUG in cases of where the contralateral kidney is normal by sonography is controversial.

Diagnosis of MCDK is usually made postnatally with a sonogram, which shows a multiloculated mass with little parenchyma (Figure 6.6). The cysts are generally nonconnected. When the cysts appear to be connected, the diagnosis of severe UPJ obstruction should be entertained. Although there are reports of familial lesions, most are sporadic and familial screening in the absence of a significant familial history is not warranted.[263] The diagnosis is confirmed with a dimercaptosuccinic acid (DMSA) scan that demonstrates no function of the affected side. Contralateral imaging with sonography to rule out obstruction or bilateral MCDK is mandatory. Ureteral atresia is associated with a higher incidence of contralateral abnormalities than is renal pelvic atresia.[264]

While previously nephrectomy was commonly performed, today serial sonography is the standard. Multicystic kidneys typically regress.[265–267] Factors predicting resolution are still under investigation. Potential predictors of resolution are right-sided lesion and initial size of <62 mm.[268,269] Rare reports of malignancy have led some to suggest that these lesions should be removed if they persist, and only lesions that involute be managed nonoperatively.[270,271] More recently, it is recognized that the likelihood of malignancy is extremely rare.[272,273] Rarely, lesions that compromise respiration or feeding or are associated with hypertension should also be excised.[274]

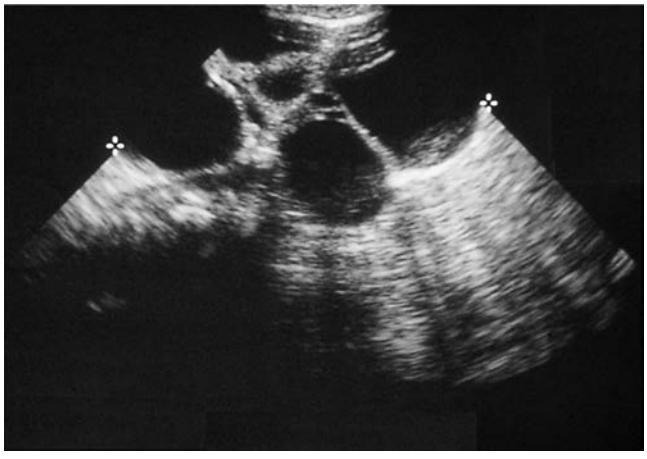


FIGURE 6.6 Sonogram of multicystic dysplastic kidney. (From Anthony Balcom, Milwaukee, WI. With permission.)

Multilocular cystic nephroma is a rare benign renal neoplasm. Lesions may be unilateral or bilateral, and bilateral metachronous lesions have been reported.[275,276] A familial association has been reported, and partial nephrectomy is being increasingly used when feasible to preserve renal parenchyma (Figure 6.7).[277,278]

Bilateral Cystic Lesions

Autosomal recessive polycystic kidney disease (ARPKD) is an inherited nephropathy with an overall incidence of approximately 1:20,000 and presents with varying degrees of severity.[279–281] Children present with massively enlarged kidneys that are typically seen on antenatal or postnatal sonograms as homogeneously hyperechogenic. In severe cases, oligohydramnios and Potter's facies may be present. The sonographic pattern is sufficiently different from that of MCDK and ADPKD to distinguish reliably between them. Pathologically, the kidneys of these children exhibit ectasia and cystic dilation of the collecting tubules. Associated conditions include pulmonary hypoplasia and hepatic fibrosis, both of which contribute significantly to morbidity. *Abnormalities of the ARPKD gene*, PKHD1, *are responsible for this disease*. Prognosis for these children depends on the spectrum of their disease, but is generally poor, with those surviving the neonatal period requiring hemodyalysis and transplantation.[282] Up to 30% of children die as neonates, with 20%–45% progressing to end-stage renal disease by age 15.[280,283] Improvements in renal replacement therapy have led to an 80% 10-year survival rate for those who survive the neonatal period, and liver disease may have the largest impact on long-term morbidity and mortality.[280,284]

*ADPKD has an incidence of 1 in 500 to 1 in 1000 births, and two gene sequences on chromosome 16 (*PKD1*) and chromosome 4 (*PKD2*) have been associated with this disorder.*[285,286] *PKD1* accounts for 64%–85% of cases and produces a more severe disease state with an earlier onset.[287,288] The proportion of *PKD2*-associated disease has increased in recent studies to 36%, likely due to increased detection of this less severe form by imaging.[288] A third locus, *PKD3*, has been proposed but remains unidentified.[281,287] While formally called "adult" polycystic kidney disease, this name is inaccurate, as 2%–5% of cases present in childhood or in utero.[281] Patients with this disease may be diagnosed by prenatal sonogram. Sonography is also the primary modality used to screen potentially affected siblings.[281,289] Infants born with this disorder often have massive renomegaly, and severely affected infants have poor survival. It is important to remember that in children, the disease may initially present unilaterally or with asymmetry. A meta-analysis of the cases identified in utero revealed that 43% of cases died before the first year of life and a significant proportion (67%) developed hypertention by age 3.[290] Children who do not present in the neonatal period often come to attention later in life with hypertension, impaired renal function, proteinuria, or hematuria. Associated conditions include hepatic and pancreatic cysts, as well as cerebral

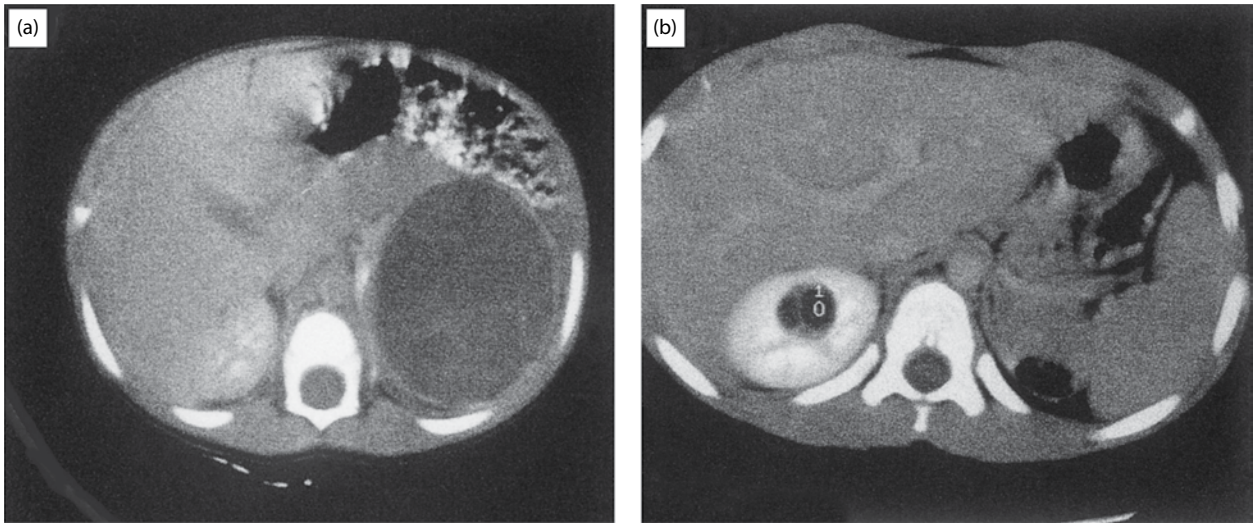


FIGURE 6.7 Multilocular cyst of the kidney (cystic nephroma). (a) CT scan of cystic nephroma in the left kidney with a normal right kidney. (b) CT scan of the same patient 2 years later with a solitary right kidney and metachronous cystic nephroma. (From Ferrer FA et al. *Urology* 1994;44:254–9. With permission.)

aneurysms. Although the outlook for these patients is improving with new targeted therapies,[291] approximately half will develop end-stage renal disease by age 60.[281,292]

Midline Cystic Abdominal Masses

As with UPJ and MCDK, modern ultrasonography has greatly facilitated the diagnosis of other less common cystic abdominal masses in infants. Previously, children would often undergo laparotomy to establish such a diagnosis.

Hydrometrocolpos refers to the distension of the vagina with mucus and blood derived from uterine and cervical glands. Produced in response to maternal estrogens, it results from vaginal obstruction secondary to imperforate hymen or other obstructive vaginal anomalies, such as transverse vaginal septum or vaginal atresia.[293,294] In patients with a mid- or high transverse septum or vaginal agenesis, a thorough search for associated genitourinary and gastrointestinal abnormalies should be performed.[295,296] It most commonly presents as a midline abdominal mass and/or an interlabial mass in the perineum, which is the bulging imperforate hymen. The diagnosis has also been made on antenatal sonography.[297–299] Careful physical examination will show that the mass is anterior to the rectum. Sonography will indicate that the lesion is behind the bladder. A common finding in these patients is LUTO and hydronephrosis.[300,301] Once the diagnosis is made, incision of the hymen and drainage result in resolution of the mass. Hydronephrosis then usually resolves with time. Care must be taken because simple percutaneous drainage may result in reaccumulation of secretions within the vagina. Serial ultrasonography should be performed to ensure that the hydronephrosis resolves. Other causes of an interlabial mass in a newborn infant include hydro(metro)colpos, prolapsed urethra, prolapsed ureterocele, and paraurethral cyst.

Ovarian cysts are the third most common cause of an intra-abdominal mass in an infant, after renal and gastrointestinal causes. They may exist in up to 30% of neonates.[302] This diagnosis has been made prenatally by ultrasound as well as postnatally.[303,304] The classic prenatal sonographic appearance is that of an anechoic, unilocolar mass in the fetal pelvis. Any internal echogenicity suggests cyst torsion or hemorrhage.[302] The majority of cysts regress and only require observation. Large cysts may compromise bowel or respiratory function. Adnexal torsion in females followed by cystic degeneration of the ovary may occur. Surgical excision of the cystic mass is typically indicated for cysts greater than 4 cm because of increased risk of torsion or heterogeneous cysts that are likely already torsed (Figure 6.8). [305]This can be accomplished by open surgery or may be achieved laparoscopically, even in infants (Figure 6.9).[306,307]

Dilation of the urinary bladder or megacystis can also result in an abdominal mass. It is most typically associated with PUVs in male infants. The classic ultrasound findings include a dilated, thickened bladder and a dilated posterior urethra ("keyhole sign"). Other potential causes include urethral atresia, megacystis–microcolon syndrome, prune

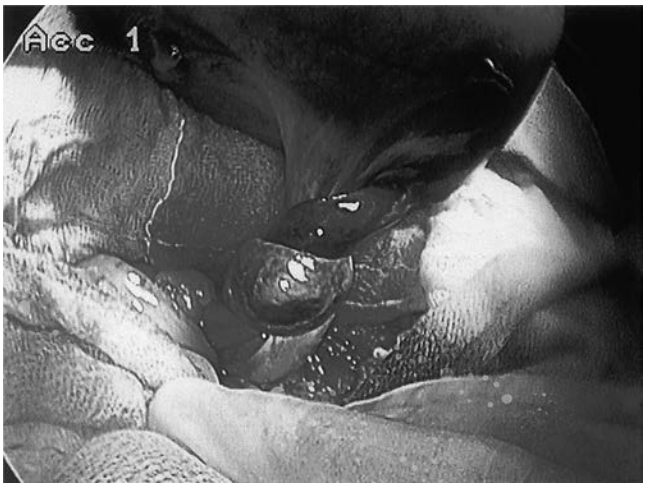


FIGURE 6.8 Torsion of the ovary presenting as a complex cyst.

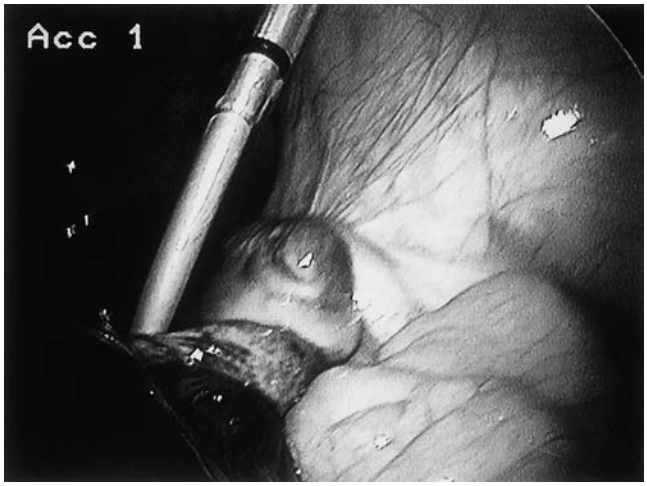


FIGURE 6.9 Laparoscopic identification of ovarian torsion.

belly syndrome, anterior urethral valves, and ureterocele obstructing the bladder outlet. Neonatal urinary ascites previously presented as an enlarged abdomen in newborns; however, today the diagnosis is frequently made in utero by antenatal sonography.[308–310]

Ascites in the fetus or newborn can be from urologic and nonurologic causes. *Urinary ascites accounts for about 30% of all cases of neonatal ascites.*[311] Among urologic causes, LUTO and trauma are most common. Specifically, PUVs, urethral stenosis, distal ureteral stenosis, anterior urethral valves, and obstructing ureteroceles have all been associated with neonatal urinary ascites (Figure 7.21).[312–317] Less frequently, obstructed and hydronephrotic kidneys may also be the cause. In these cases, extravasation of urine occurs either from the bladder or, more commonly, from a forniceal rupture in the kidney.[318] Ascites from unilateral obstructive lesions has been reported, although far less commonly than in cases of bilateral obstruction.[319,320] Alternatively, perinatal trauma to the urinary tract may also cause neonatal ascites.[321] This includes iatrogenic bladder perforation from bladder or umbilical artery catheterization.[322–324]

Sonography and VCUG can usually determine the urologic abnormality and site of extravasation in those with neonatal urinary ascites. Historically, plain film x-ray findings of a ground-glass appearance of the abdomen with floating loops of bowel have been described in patients with ascites. Neonatal urinoma, which may or may not be associated with ascites, can be identified by a "c" sign, a rim of opacified contrast around the kidney on intravenous pyelography (IVP).[325] Clinically, these patients can be quite ill. The characteristic laboratory findings include hyponatremia, hyperkalemia, and elevated serum creatinine.[326] Treatment is individualized, but urinary drainage with a urethral catheter allowing the intraperitoneal urine to be reabsorbed, along with urinary antibiotic prophylaxis, is often sufficient. Open or percutaneous drainage may be required in instances where infection of the urine occurs or when respiratory impairment is due to the mass effect. Previous reports of 70% mortality have improved to less than 15% in more recent series.[316,327–329] De Vries et al. reported the long-term follow-up of a series of patients with severe obstruction that had good lower tract and renal function.[330] Like others, the authors postulate that the development of ascites serves as a protective mechanism, allowing the kidney to decompress, minimizing damage from obstruction.[329,331–333] Nonurologic causes of neonatal ascites include erythroblastosis fetalis, cardiac or hepatic abnormalities, sepsis, and gastrointestinal perforation.[242,334]

Solid Abdominal Masses

Solid lesions in children are being detected prenatally with increasing frequency. One of the best examples is neuroblastoma.[335–337] While early detection of neuroblastoma does not necessarily change initial management, it results in the child receiving treatment sooner. In addition, patients with neuroblastomas detected early in life have a better outlook.[338,339] Thus, early diagnosis probably improves the prognosis.[335] As a rule, solid lesions detected antenatally are followed before delivery, and then after birth are imaged by CT scan or MRI. Occasionally, a postcontrast kidney, ureter, and bladder (KUB) film may clarify the diagnosis. No indications for antenatal intervention exist for solid lesions.

Neuroblastoma is the most common solid malignant tumor in neonates and is characterized by its variability in presentation.[340,341] This tumor affects 1 in 7000 children, with 40% of cases diagnosed in children less than 1 year of age.[342] The exact origins of neuroblastoma have not been elucidated, but genetic abnormalities of chromosomes 1p and 11q have been reported.[343] The tumor is often identified prenatally.[341,344–347] In addition to prenatal ultrasound, fetal MRI can contribute to the prenatal evaluation.[336,348] If not detected by prenatal imaging, many children still present with a palpable abdominal mass. *Neuroblastoma has classically been described as a firm, fixed lesion that may cross the midline. Children may also present with bulky metastatic disease that includes a palpable liver and subcutaneous nodules that characterize stage IV-S disease.* This form usually undergoes spontaneous regression.[349] Imaging by ultrasound can usually suggest the diagnosis. Confirmation is made by CT scan or MRI. Nearly half of neuroblastomas arise in the adrenal glands, with extra-adrenal retroperitoneal locations making up another 25%.[350] These studies show a lesion that displaces the kidney but does not arise from the kidney (Figure 6.10). The appearance of a tumor arising from the kidney will cause a beaking effect of the renal tissue (Figure 6.11). Despite modern imaging techniques, the diagnosis of neuroblastoma may be confused with other less common conditions, such as pulmonary sequestration.[351] Cystic neuroblastomas detected prenatally have also been reported, so the diagnosis should not be excluded on the basis of a cystic component.[352–357] Most neuroblastomas cause elevations of urinary catecholamines, which should be checked in all such patients.

The International Neuroblastoma Risk Group designed a new staging system (INRGSS), with specific image-defined risk factors (IDRFs) based on preoperative CT or MRI.[358] Histologic confirmation through tissue biopsy and serum or urine catecholamines or metabolites are also important to the staging system.[359] Many factors, including age at detection and location, affect overall outcome. In the United States, the Children's Oncology Group (COG) risk assignment, based on the International Neuroblastoma Staging System (INSS) stage, *MYCN* amplification, tumor cell ploidy (DNA index), and

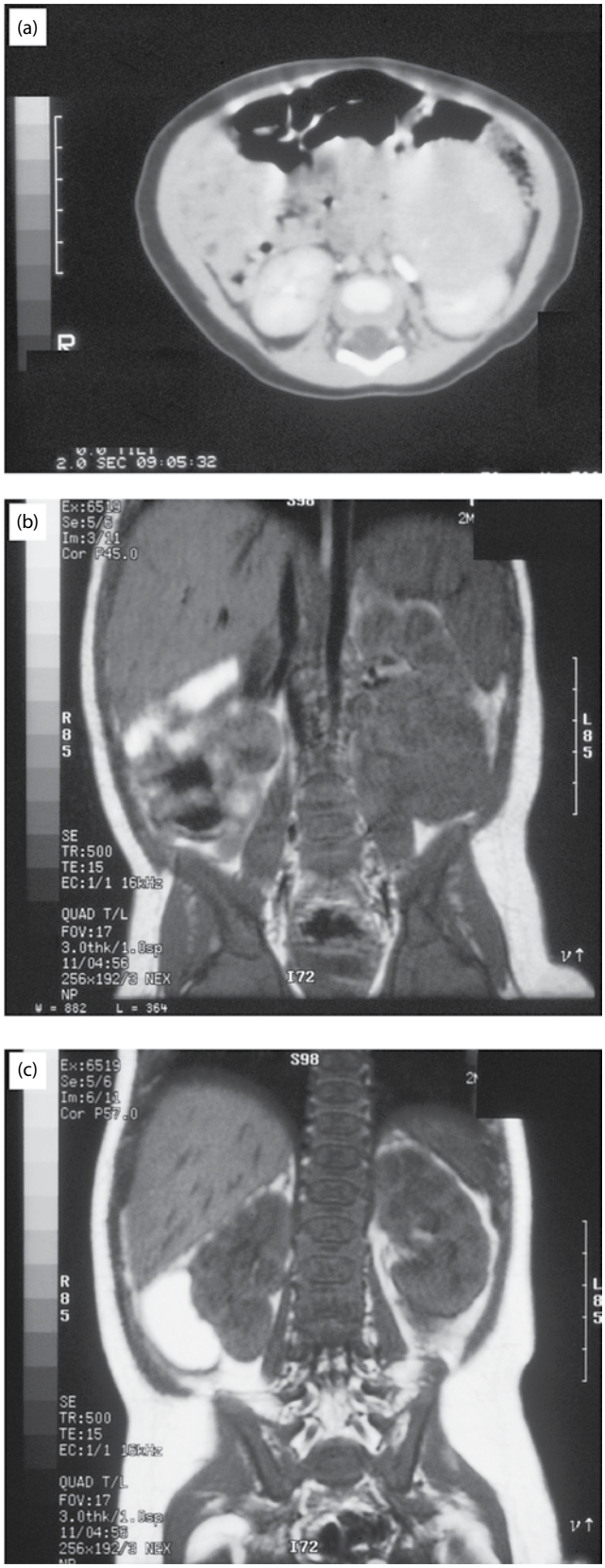


FIGURE 6.10 (a) CT scan showing displacement of the kidney by neuroblastoma (note that there is no beaking of the renal tissue). (b) MRI showing neuroblastoma in relation to the kidney. (c) MRI showing normal renal contour confirming that the tumor is separate from the kidney.

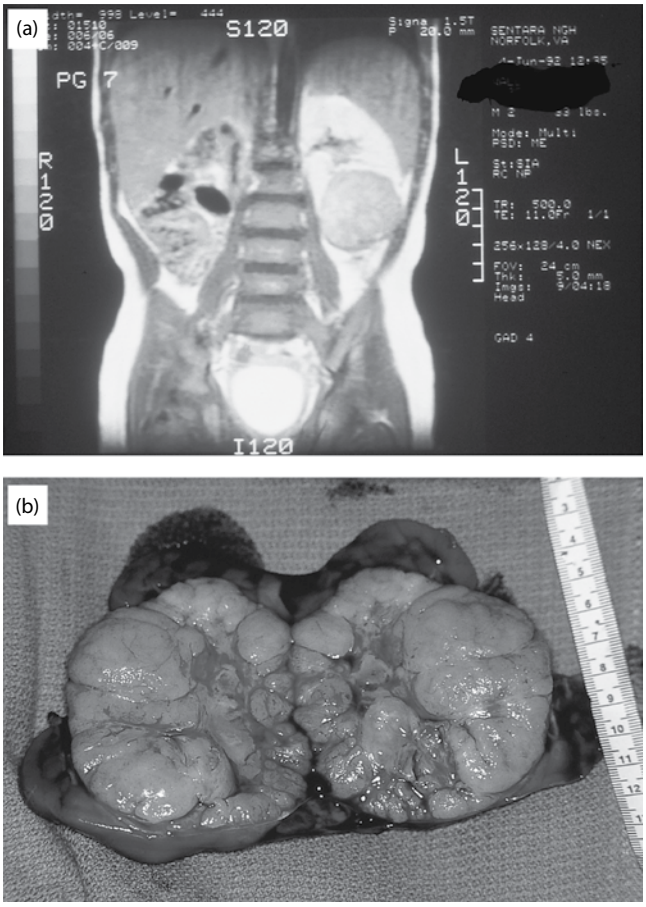


FIGURE 6.11 (a) Wilms' tumor showing beaking of the renal tissue, confirming its intrarenal location. (b) Bivalved tumor showing the beaking effect of the normal renal tissue around the mass.

histopathology (Shimada classification), is widely used to classify neuroblastoma as low, intermediate, or high risk.

Early diagnosis and treatment may be critical in some cases.[360] However, information derived from countries with mandatory postnatal screening for neuroblastoma suggests that many tumors detected in the perinatal period regress. Therefore, some infants diagnosed very early may have unnecessary interventions that do not improve mortality.[342,361–364] The COG is currently conducting an observation pilot study for children presenting with perinatal neuroblastoma. Specific inclusion criteria are age of <3 months and sonographically identified adrenal mass that is <16 mL in volume, if solid, or <65 mL if at least 25% cystic, and which does not cross the midline.

Currently, children less than 1 year of age with prenatal or perinatal detection of a neuroblastoma may potentially be observed, with surgery reserved until the patient has symptoms or the mass increases in size.[350,365] Stage 4S patients, who are by definition less than 1 year of age and have limited metastases, may also be observed initially if histology shows a lack of high-risk features. Treatment varies from observation to surgery for those patients with early-stage localized disease, but there will likely be a trend toward increasing observation.[365] Multimodal therapy, including chemotherapy and radiotherapy, is indicated in patients

with intermediate- and high-risk disease. Several clinical trials of experimental drugs continue, as prognosis for high-risk patients is still poor, even for infants.[350,366] Treatment protocols are available through the COG.[360,367–369]

Sacrococcygeal teratoma presents with an estimated incidence of 1 in 21,000 births.[370] Most are benign, but malignant transformation can take place and the incidence of malignancy increases with delayed resection.[371] The majority occurs in females, but malignancy is slightly more common in males.[372] Intrapelvic lesions may be difficult to diagnose. The presumptive in utero diagnosis has been made by ultrasound. When this lesion is suspected in the postnatal period, it is best evaluated CT or MRI.[350,373] The tumor may cause obstruction of the urinary tract with resultant hydronephrosis. Treatment typically consists of surgical excision. Serum α-fetoprotein can be elevated in malignant tumors and can aid in the detection of recurrence.[374] Long-term urologic sequelae are possible, including neuropathic bladder, and are more likely with higher lesions.[374] A detailed urologic workup, including urodynamic studies, should be performed if any suspicion for neurogenic bladder exists.

Congenital mesoblastic nephroma is a rare renal tumor that is the most common solid renal mass in children less than 6 months of age (50%). Eighty percent of these lesions are discovered in the first month of life.[375] Congenital mesoblastic nephroma may frequently be detected prenatally, where it is associated with polyhydramnios in approximately 70% of cases,[376] or may also be detected by routine child screening ultrasound in countries where this is performed.[377] Typically, the lesion is noted as a solid intrarenal mass on sonogram that appears fibroid when removed (Figure 6.12).[378] A cystic form can also occur (Figure 6.13).[375] Pathologically, the tumor can be divided into two groups: classic and cellular. The classic lesion represents one-third of cases and is microscopically similar to a leiomyoma and does not metastasize.[379,380] The cellular variant has the potential for local recurrence and metastasis and may be diagnosed slightly later in life.[377,380,381] In utero treatment usually consists of observation and management of polyhydramnios, with its attendant complications. Postnatally, nephrectomy is recommended. In cases where metastases have occurred, chemotherapy may be warranted.[381,382] Fortunately more than

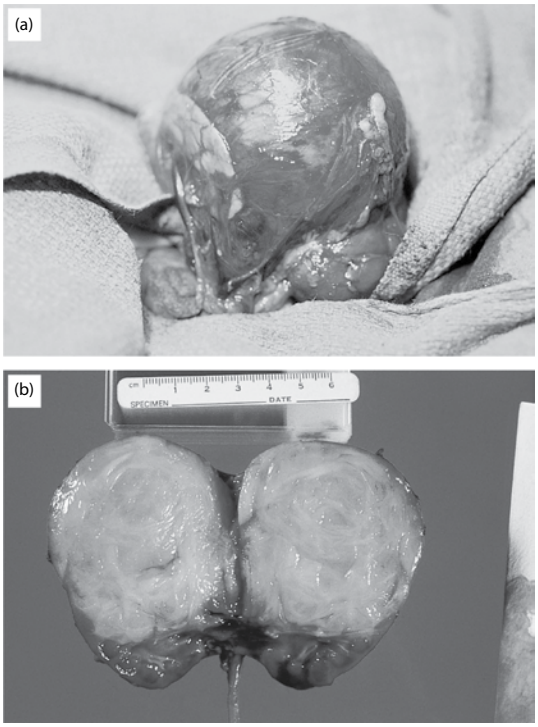


FIGURE 6.12 Solid mesoblastic nephroma in a 3-day-old patient: (a) surgical picture and (b) bivalved lesion showing a typical fibroid appearance.

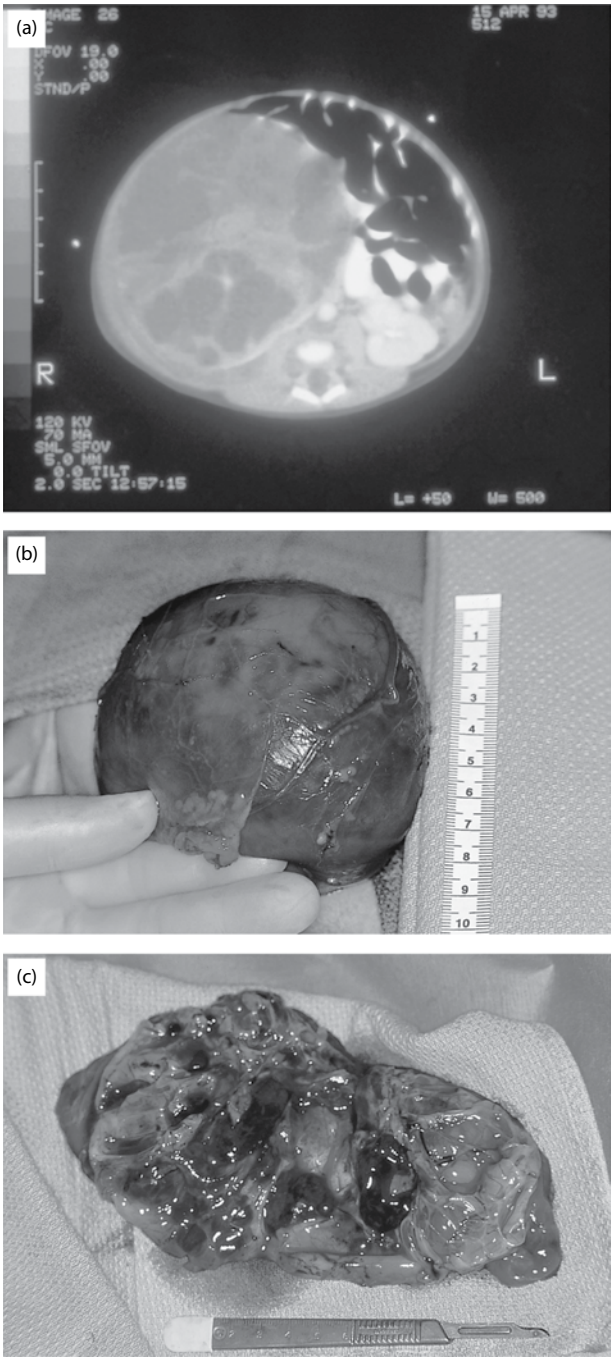


FIGURE 6.13 (a) CT scan of cystic mesoblastic nephroma. (b) Cystic mesoblastic nephroma after excision. (c) Bivalved cystic mesoblastic nephroma.

80% of tumors are low stage.[383] Hypercalcemia requiring treatment has been documented but usually resolves after nephrectomy.[381] Cases requiring urgent surgery following tumor rupture and hemorrhage have been reported.[384,385] Disease-free and overall survival are excellent, at near 95% following resection.[377,386]

Although Wilms' tumor is the most common renal tumor in children, it occurs infrequently in the neonatal period.[387,388] In children less than 6 months of age, congenital mesoblastic nephroma is a more common cause of a solid renal lesion; however, Wilms' tumors, rhabdoid tumors, clear cell tumors, renal cell carcinoma, angiomyolipoma, and ossyyfing tumors are known to occur.[383,388–390] Most of these present as a neonatal abdominal mass, and less frequently as hematuria, paraneoplastic syndromes, or hypertension.[381,391] Wilms' tumor has also been detected by prenatal ultrasound evaluation.[392–395] Associated findings in the prenatal period include fetal hydrops and polyhydramnios.[381] Postnatally, these children may have a palpable mass and, in some cases, hypertension. Children born with known associated syndromes, such as aniridia, Wilms tumor, anaridia, genitourinary anomalies, mental disability (WAGR), Denys–Drash, or Beckwith–Wiedeman, develop tumors at a younger age and are more likely to have bilateral lesions; therefore, surveillence ultrasound should be performed.[387,396] Bilateral nephroblastomatosis, aniridia, and 11p13 deletion result in the development of Wilms' tumor in close to 100% of affected individuals (Figure 6.14). These patients may develop bilateral Wilms' tumor, requiring nephron-sparing surgical techniques. Evaluation of the vascular anatomy is best performed with magnetic resonance angiography (Figure 6.15).[397]

The treatment is based on stage and the histology and genetics of the tumor. Approximately 90% of tumors have favorable histology, with the remaining 10% comprising unfavorable variants, including clear cell, anaplastic, and rhabdoid types.[350] Treatment involves surgery, chemotherapy, and sometimes radiation therapy. Debate continues over the merits of primary surgical excision with adjuvant chemotherapy and radiation based on findings, as recommended the National Wilms Tumor Study Group (NWTS), versus neoadjuvant chemotherapy prior to surgery to facilitate surgery and decrease tumor spillage, as recommended by the International Society of Pediatric Oncology (SIOP). Neoadjuvant chemotherapy is recommended by both groups for tumors that appear unresectable, have significant vascular involvement, or are bilateral.[350] The common standard chemotherapy agents utilized include vincristine, doxorubicin, and dactinomycin. Both protocols have good success rates, with overall survival rates of greater than 90%,[398] and there is a great deal of effort to maintain these results while reducing morbidity. The NWTS is currently continuing to evaluate the safety of avoiding chemotherapy in those with a very low risk of recurrence after initial results showed increased risk of recurrence but no impact on overall survival.[399] Efforts to minimize morbidity or treatment must be balanced against the success of aggressive initial

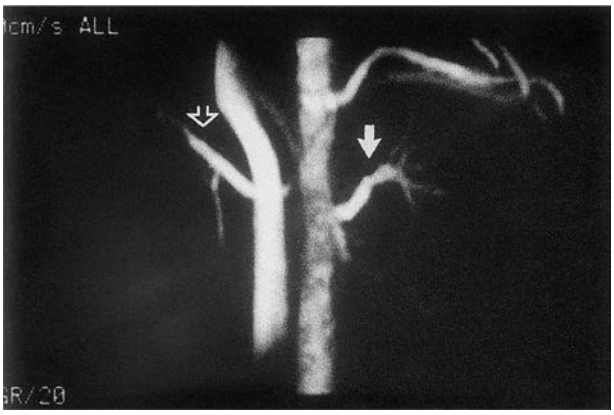


FIGURE 6.15 Phase-contrast magnetic resonance angiography. The open arrow indicates the superiorly displaced right renal artery from a Wilms' tumor. The solid arrow indicates the single left renal artery. (From Ferrer FA et al. *Urology* 1994;44:254–9. With permission.)

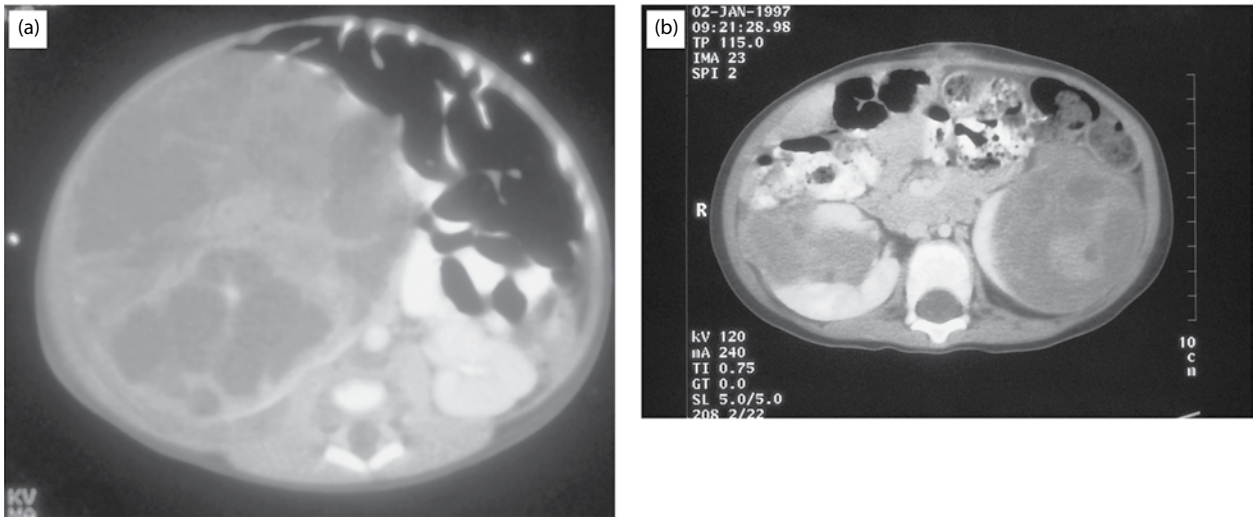


FIGURE 6.14 (a) Aniridia with red reflex. (b) Bilateral Wilms' tumor in a patient with aniridia.

treatment. Salvage therapy after recurrence is much less successful, with rates of 50% for those with favorable histology and even lower rates with unfavorable variants.[350]

Renal vein thrombosis (RVT) may be the cause of a mass in a neonate. *The characteristic clinical presentation of RVT, an enlarged kidney, hematuria, and proteinuria in an ill infant, is only present in a small percentage of patients* (Figure 6.16), but prevalence of each sign individually is near 50%.[400] Male-to-female and left side–to–right side ratios are both approximately 2:1. Seventy percent are unilateral.[400] Low platelet counts due to consumption by the developing thrombus may be seen. Infants appear to be predisposed to this condition because of lower renal arterial and venous flow rates than older children and adults. Reports of prenatal diagnoses of RVT are now commonplace.[400–402] RVT is most commonly associated with risk factors that include dehydration, sepsis, birth asphyxia, maternal diabetes, polycythemia, cardiac disease, protein C deficiency, twin–twin transfusion, and the presence of an umbilical catheter.[402,403] In addition, the significance of prothrombotic risk factors, such as factor V, are increasingly being recognized.[404,405] The thrombosis starts in the venules within the kidney and progressively extends to the major renal vein or veins. The diagnosis is most commonly made by ultrasound (Figure 7.29).[406,407] Initially, the lesion appears as highly echogenic streaks within the kidney. Subsequently, the kidney becomes enlarged and echogenic, with loss of corticomedullary differentiation.[408]

Treatment of RVT is initially supportive, with hydration and correction of any predisposing abnormalities.[407,409] Recent guidelines from the American College of Chest Physicians (ACCP) recommend unfractionated or low-molecular-weight heparin therapies for the treatment of unilateral RVT with extension into the inferior vena cava.[410] Initial thrombolysis with tissue plasminogen activator and anticoagulation therapy with unfractionated heparin, followed by continued anticoagulation with unfractionated or low-molecular-weight heparin, is recommended for those with bilateral thrombus.[410–412] Certain studies have suggested that those who receive aggressive therapy with anticoagulants fare better than those who do not,[402] but either supportive care alone or heparin is acceptable for unilateral RVT.[410] Optimal treatment for unilateral RVT in the setting of renal impairment or prothrombotic factors is not defined.[407]

Patients with unilateral thrombosis usually do well, while those with bilateral thrombosis have a higher rate of complications, such as renal failure.[400,413] Approximately 20% of patients will have persistent hypertension, and all patients must have long-term monitoring of renal function and evaluation for hypertension.[400,414,415]

Renal artery thrombosis does not commonly present as a neonatal mass but may be a cause of renal failure if bilateral.[416,417] The occurrence of this disorder has increased significantly in relation to the increased use of umbilical artery catheters, despite the fact that a causal relationship was identified some time ago.[418] Recent research has suggested that both short- and long-term umbilical artery catheterization may produce pathologic changes in the arterial wall.[419] The diagnosis is commonly made with Doppler ultrasound, which demonstrates the absence of flow in the renal artery, but CT has made the diagnosis when ultrasound was normal.[420] Treatment options include supportive measures, antithrombolytics, and surgery, depending on the extent of thrombosis and whether aortic involvement exists.[421–423]

Neonatal adrenal hemorrhage is associated with traumatic or difficult labor, neonatal hypoxia, septicemia, RVT, or coagulopathy.[424] Traditionally, it is believed that the relatively large size and vascularity of the newborn gland predisposes it to bleeding. Presenting signs include neonatal jaundice, paleness and/or flank mass, discoloration of the scrotum, and hypotonia or lethargy or hypotension.[425] Screening ultrasound examination gives an

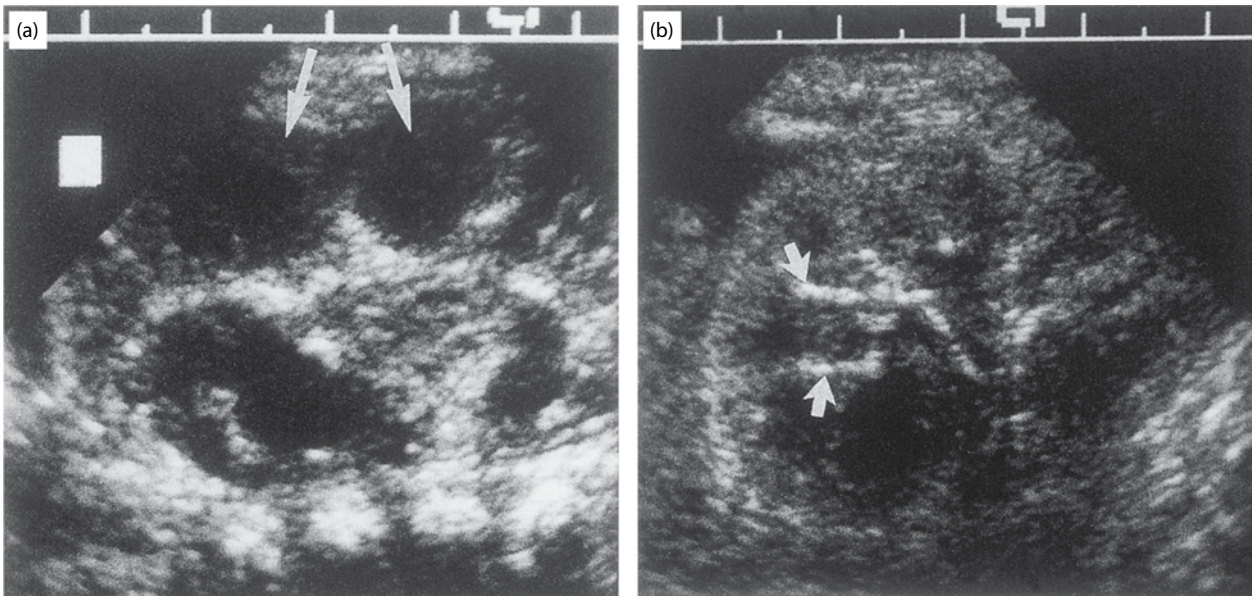


FIGURE 6.16 RVT. (a) Enlarged left kidney with echogenic intermedullary streaks and echopoor medullary pyramids (arrows). (b) Same patient's right kidney showing swelling of the upper pole and focal echogenic intermedullary streaks. (From Hibbert J et al. *Br J Radiol* 1997;70:1191–4. With permission.)

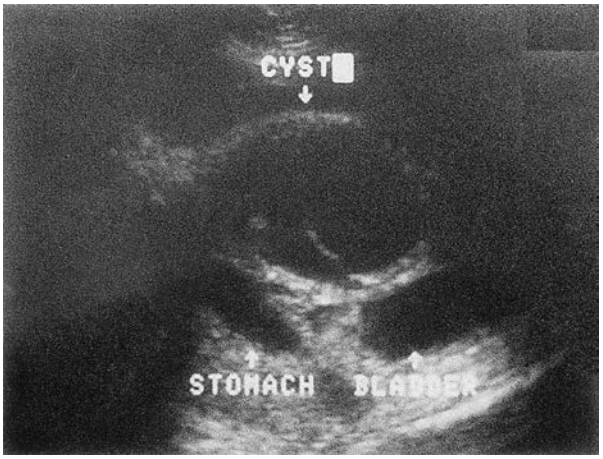


FIGURE 6.17 Prenatal adrenal hemorrhage identified as a complex cyst on sonogram. (From Burbige KA. *J Urol* 1993;150:1867–9. With permission.)

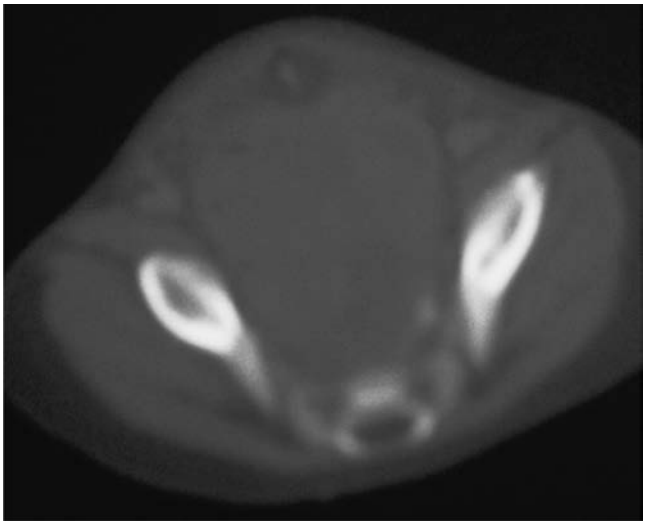


FIGURE 6.19 Pelvic sarcoma with displacement of the bladder superiorly. Note the Foley balloon in the bladder.

estimate incidence of 1.9 per 1000 births.[426] There is a right-sided predominance, and 10%–15% present bilaterally.[425,426] Diagnosis is usually made by ultrasound,[424] and antenatal diagnosis has been made in the second and third trimesters (Figure 6.17). Identification by ultrasound is usually reliable, but in some cases, it is difficult to differentiate from an adrenal neuroblastoma (Figure 6.18).[427–429] In difficult cases, CT and MRI may be helpful in the diagnosis.[430,431] Negative urine catecholamines also support the diagnosis of adrenal hemorrhage.

Experience has confirmed the initial belief that the majority of infants with adrenal hemorrhage require no treatment except for occasional phototherapy and, rarely, transfusion.[425,432,433] Resultant adrenal insufficiency has been reported in cases of bilateral hemorrhage[434] but overall is uncommon.[424] Observation for resolution and monitoring of hematocrit and bilirubin should be routine. Rarely, steroid replacement for temporary adrenal insufficiency is required.

Rhabdomyosarcoma is an uncommon neoplasm of the lower urinary tract in children. Lesions may occur in the bladder, prostate, vagina, or uterus (Figure 6.19). Presentation in infancy depends on the organ of origin and may include hematuria, vaginal bleeding, or obstruction of the urinary tract. Treatment is multimodal, with chemotherapy typically used as the primary treatment and radiation therapy and surgery used for local control.[435–437] As a result of collaborative efforts by the Intergroup Rhabdomyosarcoma Study, treatment results for these patients have improved dramatically in the last 40 years. Current efforts are focused on improving results in high-risk patients by use of additional chemotherapy agents and reducing treatment-related morbidity and mortality in all groups.[437–440] Debate continues over the merits of radical versus more conservative surgery,[440–442] but there is a trend toward less radical surgery in recent years.[437]

Gonadal tumors are rare in children, and their presentation as a lower abdominal mass is extremely uncommon. They may occur as an ovarian mass or as a mass in an undescended testis.[443–445] Mature teratomas are by far the most common tumor in both ovaries and intra-abdominal testes, followed by immature teratomas, and germ cell

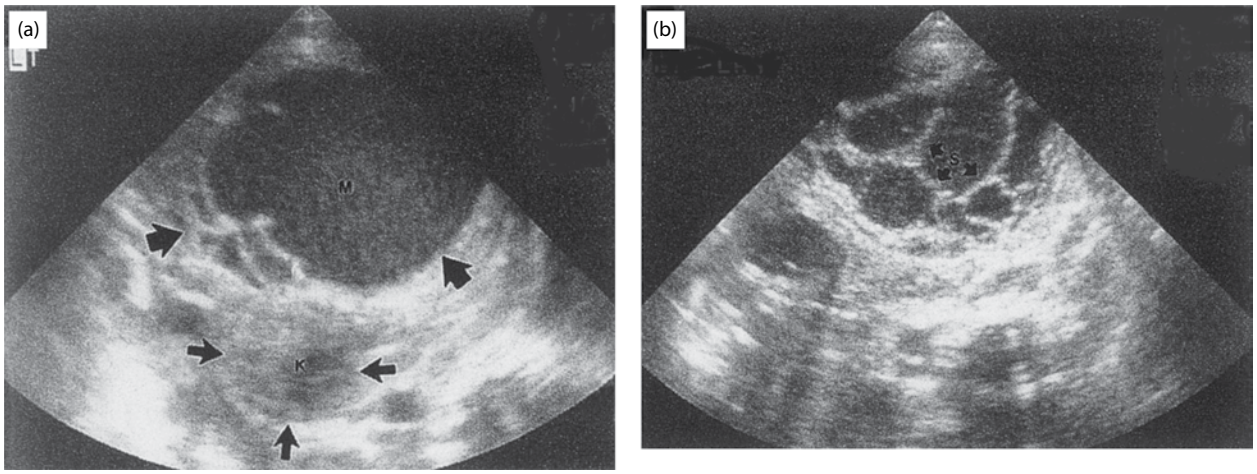


FIGURE 6.18 Postnatal confirmation of a complex cystic lesion superior to the kidney. Surgical exploration later confirms adrenal hemorrhage. (From Burbige KA. *J Urol* 1993;150:1867–9. With permission.)

tumors.[446–448] Treatment for these tumors is dependent on stage and histology. Multimodal therapy may well include surgery, chemotherapy, and radiation, which may be indicated for aggressive tumors.

SCROTAL MASSES

Identification of a scrotal mass commonly results in an urgent consultation. In the nonverbal infant less than 1 year old, pain will likely present with inconsolability, but otherwise, history plays very little role.[449]

The specific differential diagnosis of neonatal scrotal masses includes

- Hydrocele
- Lesion secondary to patent processus vaginalis (hernia or hydrocele and meconium)
- Perinatal torsion
- Paratesticular abscess
- Testis tumor

The physical examination should focus on identifying the location of the mass in relation to the testis and the orientation of the testis. Careful palpation will identify torsion of appendices, such as the appendix testis, both anterior and superior appendices of the epididymis, and the hydatid of Morgagni, which is located in the posterior inferior epididymal testicular ridge.[450] If the mass is large enough as to obscure palpation of the testis, then transillumination is helpful since it rapidly discriminates solid from fluid-filled masses. Occasionally, a plain abdominal film may be helpful in identifying bowel gas in the scrotal mass that would indicate an inguinal hernia with bowel in the scrotum, or calcification suggesting old meconium. If the mass is associated with thickened cord structures, or if it can be reduced, a hernia is also likely.

Ultrasound examination can differentiate solid and cystic masses, as well as the mass's relationship to the testis and epididymis, but is generally unnecessary since most masses represent hydroceles. Doppler ultrasound can often confirm blood flow, but can be misleading in the small child.

Hydroceles are the most common scrotal masses and can be associated with a patent processus vaginalis (communicating hydroceles or hernias). They may be unilateral or bilateral, and sometimes alarmingly large. Other lesions that result from a patent processus vaginalis include meconium mass, hemoscrotum from intra-abdominal hemorrhage, and tumor seeding from renal or adrenal tumors.[451–455] Spontaneous rupture of the bowel can occur during fetal development, resulting in meconium peritonitis. If the processus vaginalis is still open at that time, the meconium can fall into the scrotum and present as a solid mass at birth. Stippled calcification is usually present. Likewise, other anomalies, such as adrenal hematomas, neuroblastoma, and Wilms' tumor, can also seed the scrotum through a patent canal and should be considered in the differential diagnosis of neonatal scrotal masses. All these suggest the utility of abdominal ultrasonography upon discovery of the scrotal mass.

Perinatally, firm bilaterally enlarged scrotal masses may be hydroceles, but the diagnosis of *bilateral perinatal testis torsion* should be considered.[456,457] Perinatal torsion is comprised of both prenatal and neonatal torsion. Prenatal testis torsion is also referred to as extravaginal torsion, intrauterine torsion, and antenatal torsion and occurs before birth. There is controversy over the mechanism of the torsion, risk of bilaterality, and need for and timing of contralateral fixation.[458–461] When torsion occurs before delivery, it has been thought to occur extravaginally, involving the entire spermatic cord and its tunics. Some physicians believe that this process can occur very early in the pregnancy, and that it is responsible for most instances of testicular agenesis.[462–464] It is impossible to determine whether all cases are extravaginal, and at least some probably represent intravaginal torsion, as seen in older boys. When torsion occurs prior to delivery, the presentation is one of a nontender, discolored, solid scrotal mass. Doppler ultrasound is generally accurate in confirming the diagnosis.[465–469] The torsion is most often unilateral, but more than 45 bilateral cases have been reported.[459,467,470–485] In cases of suspected bilateral torsion or an initial presentation of unilateral torsion followed by any acute scrotal changes, emergent surgical exploration is clearly indicated.

Unilateral prenatal torsion with an apparently normal contralateral testis is more controversial. Some favor delayed contralateral fixation after 1–3 months.[475,486] The reasons for this approach include risks of neonatal anesthesia, a low likelihood of bilateral torsion, and the ability to diagnose contralateral torsion by clinical exam. Parents are instructed to monitor the child closely at every diaper change for any acute scrotal changes. If this approach is taken, it is important to document contralateral blood flow by Doppler. Others favor early surgical exploration on an emergent or urgent basis in any case of perinatal torsion, including unilateral prenatal torsion.[486,487] A strong case has been made for early exploration, with orchiectomy when the testis is necrotic, and contralateral fixation, as many examples of subsequent contralateral torsion have now been reported.[488–490] Other arguments for early exploration include the relative safety of anesthesia in the neonatal period; the possibility of testicular salvage (10%), particularly the hormonal function; and the confirmation of diagnosis. Additionally, recent studies suggest that 36%–50% of contralateral testes found to be ischemic at the time of surgery showed blood flow on preoperative Doppler studies.[471,487] There will likely be no clear consensus anytime soon. Indeed, a recent survey of pediatric urologists found that 10% preferred immediate exploration, 57% preferred delayed exploration, and 33% preferred observation alone.[461] The best approach in any particular scenario needs to take into account many factors, including access to specialized pediatric anesthesia teams and NICU support.

Testis tumors are also seen in the neonatal period extremely rarely. Historically, yolk sac tumors were reported to be the most common testicular tumor in the newborn period.[491] These data may have been biased however, and recently data have suggested that most prepubertal testicular tumors are benign, with teratoma being the most common (Table 6.5).[492–496] Data specific to the newborn period are not available from these studies. Extrapolating from the average age of the patients, some

TABLE 6.5 Prepubertal testicular tumors (% incidence by publication)

	Levy et al.[491]	Metcalfe et al.[492]	Pohl et al.[494]	Shukla et al.[493]	Bujons et al.[495]	Wang et al.[496]
Teratoma	5	43	48	29	13	51
Yolk sac	27	8	15	21	7	33
Gonadal stromal	27	4	13			3
Juvenile granulosa cell	27				7	
Gonadal blastoma	9	2	2		7	
Hamartoma	5				7	
Epidermal cyst		10	14	13	27	6

studies would suggest yolk sac tumors to be more prevalent in younger patients,[492] while others do not suggest this difference.[496] Regardless, the proportion of benign tumors appears higher than previously thought, and testis-sparing surgery is increasingly being utilized.[492–498] Fortunately, a tumor's malignant potential can typically be identified by preoperative imaging and serum α-fetoprotein.[492,493,495,496,498,499] As long as proper precautions are taken to allow for radical orchiectomy in the rare event of an unexpected malignant tumor, long-term outcomes for testis-sparing surgery have been good.[492–496,498] Early radical surgical removal is the recommended treatment for those with malignant potential, with chemotherapy in selected cases.

Paratesticular abscesses mimicking torsion have been reported but are very rare. Causative organisms include *Staphylococcus*, *Salmonella*, and *Klebsiella*. Methods of scrotal contamination include hematogenous, urinary, and peritoneal via patent processus vaginalis, or direct contact.[500–502] Drainage of the abscess is typically accomplished by scrotal exploration. Initial broad-spectrum antibiotics should be tailored to culture when available.

BLADDER EXSTROPHY–EPISPADIAS COMPLEX

The prenatal identification of the bladder exstrophy–epispadias complex is uncommon due to the rarity of the disease and an estimated 10%–25% detection rate by prenatal screening sonography (Figure 7.6).[503–505] However, the pediatric urologist may be called on to consult prenatally regarding postnatal treatment and outcomes.

The five most commonly identified sonographic findings are (1) no visualization of the bladder, (2) a lower abdominal bulge, (3) a small penis and anteriorly placed scrotum, (4) a low-set umbilicus, and (5) abnormal widening of the iliac crests.[505] Omphaloceles are usually associated with a midline defect at the umbilical insertion; gastroschisis most frequently consists of a small, right-sided paraumbilical defect; and large lateral defects usually occur in the limb–body wall complex. In addition, specific organ evisceration and other associated abnormalities assist in the differential diagnosis.[506,507] Prenatal ultrasound at 20 weeks' gestational age may be unable to determine gender in up 80% of cases.[503] Fetal MRI is being increasingly used in the prenatal diagnosis and to provide more accurate detail in cases of exstophy.[503,508,509]

The challenge in the prenatal identification of these abnormalities, as with any prenatal diagnosis, is to provide counseling that is both timely and accurate based on the information available regarding a particular case and the condition as a whole.[510,511]

At birth, an exstrophic bladder, an abdominal wall defect, epispadias, pelvic diastasis, VUR after bladder closure, and bilateral inguinal hernias characterize the anomaly. The infant is otherwise healthy. The best approach is to involve a physician familiar with the immediate and long-term outcome of patients with these complex reconstructive problems, who should coordinate the initial management and transfer, if the baby is born at an outside institution. The initial treatment is to protect the exposed bladder mucosa. If a plastic umbilical clamp was placed in the delivery suite, it should be removed and replaced with a suture. If possible, nothing should come into contact with the bladder mucosa. A modified humidifier tent can be placed over the bladder, but for transport, a cellophane nonadherent dressing may be utilized, while gauze or petroleum products should be avoided.[512] Transfer to a center with exstrophy experience should be considered soon after birth but is not emergent, and the child should be stabilized and adequately hydrated before travel.[512] The protection afforded by cellophane dressings is adequate enough that it has been utilized to allow patients to be discharged home prior to surgery to allow growth and parental bonding.[513] An increased risk of latex allergy has been reported in patients with urologic abnormalities, such as exstrophy, and appears to increase as the number of surgeries increases. Exstrophy patients should be cared for in latex-free environments to minimize this risk, which can have serious consequences, such as intraoperative anaphylactic reactions.[512,514,515]

Controversy continues regarding complete primary repair versus modern staged reconstruction,[516] although complete primary repair is becoming increasingly utilized.[517–519] Enthusiasm for the possibility of fewer surgeries and promotion of early bladder cycling led to increasing adoption of complete primary repair of exstrophy (CPRE) developed by Dr. Michael Mitchell.[517–520] Continued diffusion of this technique has been somewhat tempered by increasing reports of ischemic penile injuries and the fact that subsequent procedures may still be required.[521,522] The more traditional staged repair[523,524] is the most studied, with the longest reported outcomes. The first stage

involves bladder and abdominal wall closure with pelvic osteotomy in most cases (Figures 6.23 and 6.24).[523,524] Other reconstructive strategies have also been used, including the Kelly repair,[525] the Warsaw approach,[526] and the Mainz II pouch,[527] and bioengineered tissues may play a role in the future.[528,529] Exstrophy reconstruction and new imaging modalities have led to a greater understanding of sphincter and pelvic floor anatomy and function.[530,531] Patients have improved pelvic floor reconstruction and better continence rates after osteotomy.[532–535] This is likely due to better approximation of the pelvic floor muscle. In addition, there is a close relationship between bladder size and continence. In situations where capacity is inadequate, bladder augmentation, bladder neck closure, and a catheterizable stoma may provide the best alternative.[536–538] Debate over which reconstructive technique provides the best long-term outcome will continue, but has little impact on the immediate neonatal care, which focuses on bladder protection, parental counseling, and timely referral to a center with exstophy experience.

Regardless of the technique employed, a complete understanding of the underlying anatomical abnormalities and the surgical approach is a requirement for the appropriate counseling of prospective parents to help them understand what will be involved in the early life of these patients. Long-term data, including the psychosocial and physical outcomes of patients treated with various surgical approaches, continue to accumulate, but patient numbers are still small. Quality of life tends to be near normal in regard to education, family life, employment, and social interactions.[539–542] The males were concerned about the appearance of their external genitalia,[543] even though their sexual function was preserved.[544] The female patients were less concerned about disfigurement and had normal sexual function and sexuality.[545] Fertility can often be achieved for men and women with exstrophy but may require assisted reproductive techniques.[545–547]

PRUNE BELLY SYNDROME

Deficient abdominal wall musculature, cryptorchism, and urinary tract dilation characterize this syndrome. Other names include triad syndrome, Eagle–Barrett syndrome, and abdominal muscular deficiency syndrome. The presumptive prenatal diagnosis has been made as early as 11–14 weeks' gestation and is becoming more common with improved imaging techniques.[548–550] Keys to the antenatal diagnosis include distended thin-walled bladder, stenosis or dilation of the entire urethra, and hydronephrosis and hydroureter with or without oligohydramnios.[549,551] Posterior urethral valve (PUV) can sometimes be distinguished from prune belly syndrome (PBS) by a thickened bladder wall or a keyhole sign, but the distinction can be difficult, especially when oligohydramnios occurs.[99,552] One terminated fetus had urethral atresia with histologically normal kidneys.[553]

The overall incidence is approximately 3.8 per 100,000 live male births, with black children affected at a disproportionately high rate.[554] The spectrum of this disease is wide. Although predominantly affecting males, a female variety has been described.[555–557] It ranges from in utero demise to renal dysplasia and subsequent renal failure to normal renal function. The in-hospital mortality rate is nearly 30% for those born with PBS and has not significantly improved in recent decades.[554] The pathogenesis is not completely understood,[558] but a high concordance rate in twins, apparent familial patterns, and varying incidence between ethnic groups point to a genetic component.[554,559–562] Limited data have implicated the *HNF1B* gene on chromosome 17q12,[563,564] but clear evidence of its effect is still lacking.[565]

Antenatal intervention with vesicoamniotic shunting[566] or serial vesicocentesis and amnioinfusions[567] have been described and may gain increasing use with improved prenatal diagnosis and advancement of fetal intervention. The postnatal evaluation should include physical exam, urinalysis and urine culture, serum creatinine and electrolytes, sonography, VCUG, and renal scan when indicated, although VCUG can be avoided to reduce the risk of early UTI.[568–570]

Initially, medical treatment (i.e., antibacterial prophylaxis and perhaps circumcision in babies with reflux) and close surveillance are indicated in all but the most severe cases, where vesicostomy or upper tract diversion may be needed.[550,570–574]

In the long term, a combination of continuous antibacterial prophylaxis, well-planned surgery, and close surveillance is the best means to ensure an optimal outcome.[550,570,572,574–578] The severity of the congenital renal dysplasia, a nadir creatinine greater than 0.7 mg/dL, recurrent pyelonephritis, and renal obstruction all correlate with eventual development of renal failure.[496,576]

Treatment of the undescended testes should be similar to that recommended for other patients with abdominal testes.[550] Early orchidopexy should be accomplished and may be facilitated by laparoscopy.[579,580] Patients requiring Fowler–Stephens orchidopexy will typically still have adequate testicular health for spontaneous puberty and sexual function.[581]

No prune belly patient has been known to father a child without assisted reproductive technologies. However, early testis biopsy has identified spermatogonia,[582,583] and there has been one report of successful pregnancy following intracytoplasmic sperm injection.[584] The histologic findings of significantly reduced spermatogonia and marked Leydig cell hyperplasia suggest that the pathology of the testis in prune belly syndrome is secondary to more than just its abdominal location. Testis tumors have developed in these patients.[585–587]

ANORECTAL MALFORMATIONS

Anorectal malformations (imperforate anus) are congenital lesions of the cloaca that are often associated with urological abnormalities (Figure 6.20). There is also a high incidence of other congenital abnormalities associated with such malformations as part of the *VACTERL (vertebral anorectal cardiac tracheoesophageal renal and limb) syndrome*. There are multiple classification systems, but from a urologic perspective, the simple distinction of "high," "intermediate," or "low" anorectal lesions is probably sufficient. Low lesions are those that occur inferior to the levator muscles, high lesions occur above the levator muscles,

FIGURE 6.20 Patient with imperforate anus. (From Dr. Donald W. Hight, Connecticut Children's Medical Center, Hartford. With permission.)

FIGURE 6.21 Radiographic picture of high bowel–urethral fistula. (From Dr. Donald W. Hight, Connecticut Children's Medical Center, Hartford. With permission.)

and intermediate ones in between (Figure 6.21).[588] From a clinical point of view, most intermediate lesions are treated as high lesions. The surgical correction of these malformations is most often by a technique popularized by de Vries and Pena[589] using the posterior sagittal approach.[590,591] Laparoscopic repair has been developed in hopes that a minimally invasive technique would improve functional outcomes by minimizing trauma and scarring to the sphincteric muscles.[591,592] To date, significant clinical evidence demonstrating this benefit has yet to be shown.[593]

Associated urologic abnormalities occur in up to 20% of patients with low lesions and up to 60% of those with high lesions, although rates appear to be higher with demonstrated chromosomal abnormalities, particularly terminal delation of 13q.[594–596] The most common findings are VUR, neuropathic bladder, renal agenesis, renal dysplasia, and cryptorchidism. Female patients may have associated hydrocolpos and obstructive uropathy requiring urgent urologic intervention.

It is not surprising that there is a high incidence of neuropathic bladder given the association of vertebral abnormalities, most commonly a tethered cord, especially with high lesions. The overall incidence of neuropathic bladder may be as high as 50%, and is more common with high and complex lesions.[594,597,598] The significant morbidity and mortality from associated renal insufficiency underscore the importance of the urologist's role in patients with anorectal malformations.

All patients should be evaluated with a renal bladder sonogram and VCUG at birth, regardless of the height of the defect. Spinal ultrasound or MRI is often needed, as occult defects, such as tethered cord, can be missed on plain films.[599,600] Evidence of neuropathic bladder has been demonstrated even in patients with low lesions and normal spinal imaging.[598,601] Urodynamics should be performed on children with high lesions, spinal abnormalities, or other suspicion of abnormal voiding, such as dilated upper tracts on ultrasound.[598] Specific treatment will then be based on urodynamic findings, as in other cases of neuropathic voiding dysfunction.

CIRCUMCISION INJURIES

Despite continued controversy over the risks, benefits, and ethics of circumcision, it remains the most common surgical procedure in newborns, with approximately 1.2 million operations performed annually in the United States. After a rise in circumcision rates in the United States during the 1990s, from ~48% to ~61%, rates declined to ~55% by 2004 and have held essentially stable since. There are significant regional differences, with only 24.6% of newborn males being circumcised in the western states.[602] Absolute indications for neonatal circumcisions are few.[603,604] Circumcision in infants with known bleeding disorders, hypospadias, and congenital anomalies of the penis; buried penis; or prematurity should be delayed to a later date.[605] In neonates with prenatally detected hydronephrosis, especially when reflux is identified, circumcision may be recommended because it decreases the likelihood of an early UTI.[109,606,607] Reports demonstrating a marked change in the periurethral and glanular

bacterial flora in boys after circumcision support this practice.[608] Indications for circumcision in older children include persistent phimosis, paraphimosis, and recurrent balanitis. A viable alternative to circumcision in infants and older children is the use of steroid cream.[609–611] This is typically accomplished by applying betamethasone cream (0.05%–0.2%, with or without the addition of hyaluonidase) to the prepuce twice daily for 4–8 weeks. Success rates of roughly 70%–90% have been reported. Topical therapy may be less effective when there is balanophostitis or a lack of meatal exposure.[612] Paraphimosis is typically treated first with pressure on the edemetous preputial skin and reduction of the paraphimotic skin. Subcutaneous injection of hyaluronidase (150 U/cc) after topical anesthetic, such as EMLA cream (2.5% prilocaine and 2.5% lidocaine; Astra Pharmaceuticals, Westboro, Massachusetts), has also been used with excellent results. The hyaluronidase reduces the edema almost immediately, facilitating an easier and less painful reduction of the foreskin.[613] Complications related to hyaluronidase injection are very rare, but isolated cases of anaphylaxis, shock, and hypovolemia have been reported when the medication is given intravascularly. If the glans cannot be replaced, a dorsal slit incision in the phimotic skin allows reduction.

Complications of circumcisions are infrequent, occurring in 0.2%–3% of cases.[614]

1. Acute complications
   a. Bleeding
   b. Infection
   c. Laceration
   d. Amputation, usually partial
   e. Urinary retention
   f. Skin loss
   g. Necrosis, sometimes due to overuse of cautery
   h. Necrotizing fasciitis
2. Nonacute complications
   a. Skin excess
   b. Skin asymmetry
   c. Skin bridges
   d. Skin chordee
   e. Epidermal inclusion cysts
   f. Concealed (buried) penis
   g. Phimosis
   h. Meatal stenosis
   i. Urethrocutaneous fistula
   j. Circumcision despite hypospadias, removing skin needed for repair
   k. Plastibell specific
   l. Lymphedema

The majority of circumcision complications are minor.[615–622] The incidence of complications is probably higher than reported in the urologic literature since many are treated without referral and some do not present until the patient is much older. *Complications are best prevented by strict attention to the details of the procedure, which include sterile technique, hemostasis, protection of the glans, and removing the appropriate amount of inner and outer preputial skin.*[623–625]

Certain anatomic variations may predispose to complications during neonatal circumcision. Mayer et al. suggested that a prominent fat pad, penoscrotal webbing, or prematurity is associated with a higher incidence of circumcision complications.[626] When complications occur, immediate attention and treatment is the best management.[627–631]

Bleeding is best managed by pressure, placing an absorbable stitch, or with electrocautery, although electrocautery should never be used with a metallic clamp device in place because of the risk of penile necrosis. Most of the cases that require immediate repair involve laceration or amputation of a portion of the glans (Figure 6.22). Commonly, these result from a circumcision done using a Mogen clamp placed at an angle incorporating the frenulum, which draws up the glans into the clamp.[629] If the amputated portion of the glans can be retrieved, it can be reapproximated with absorbable sutures. When amputation occurs, the amputated portion of the glans should be wrapped sterilely and kept cool on ice, but not submerged in saline. In most instances, it can be reattached utilizing long-lasting absorbable sutures.[628,629,631,632] Amputation of a portion of the penis involving the urethra should also be repaired by immediate reconstruction.[633] Results are best if reapproximation occurs within hours of the injury; however, successful reapproximation after delays of up to 18 hours have been reported.[634] Most urethral injuries should have a staged reconstruction, although fistulae can be closed immediately if recognized[630] (Figures 6.23 through 6.33).

Penile skin loss as a result of circumcision can usually be managed conservatively by application of antibiotic impregnated gauze. Ingrowth of skin usually results in a good cosmetic appearance. Skin grafting is rarely necessary.

Sometimes an apparently normal penis with a complete circumferential prepuce is found to have a hypospadiac meatus when the skin is incised or retracted. This rare form of hypospadias is called megameatus with intact prepuce. The circumcision should be discontinued and any remaining skin left attached for possible later use in hypospadias repair. Plastibell circumcisions have their own specific complications, including a higher incidence of delayed wound infections and retained plastic cuff. Concealed or buried penis can result when the glans penis recedes below the circumcision scar and the scar then contracts[635] due to insufficient removal of inner prepuce.

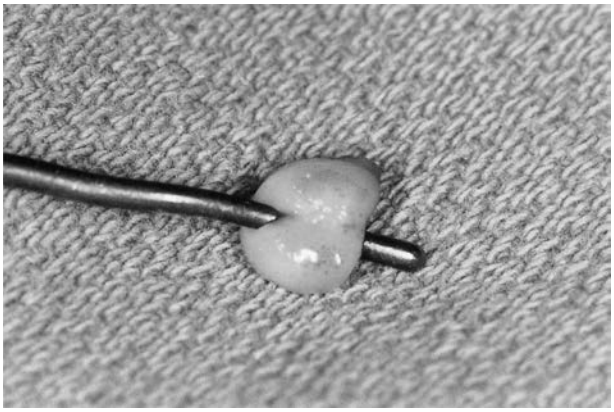


FIGURE 6.22 Amputation of the distal portion of the glans shown with urethra intubated. This was successfully reattached.

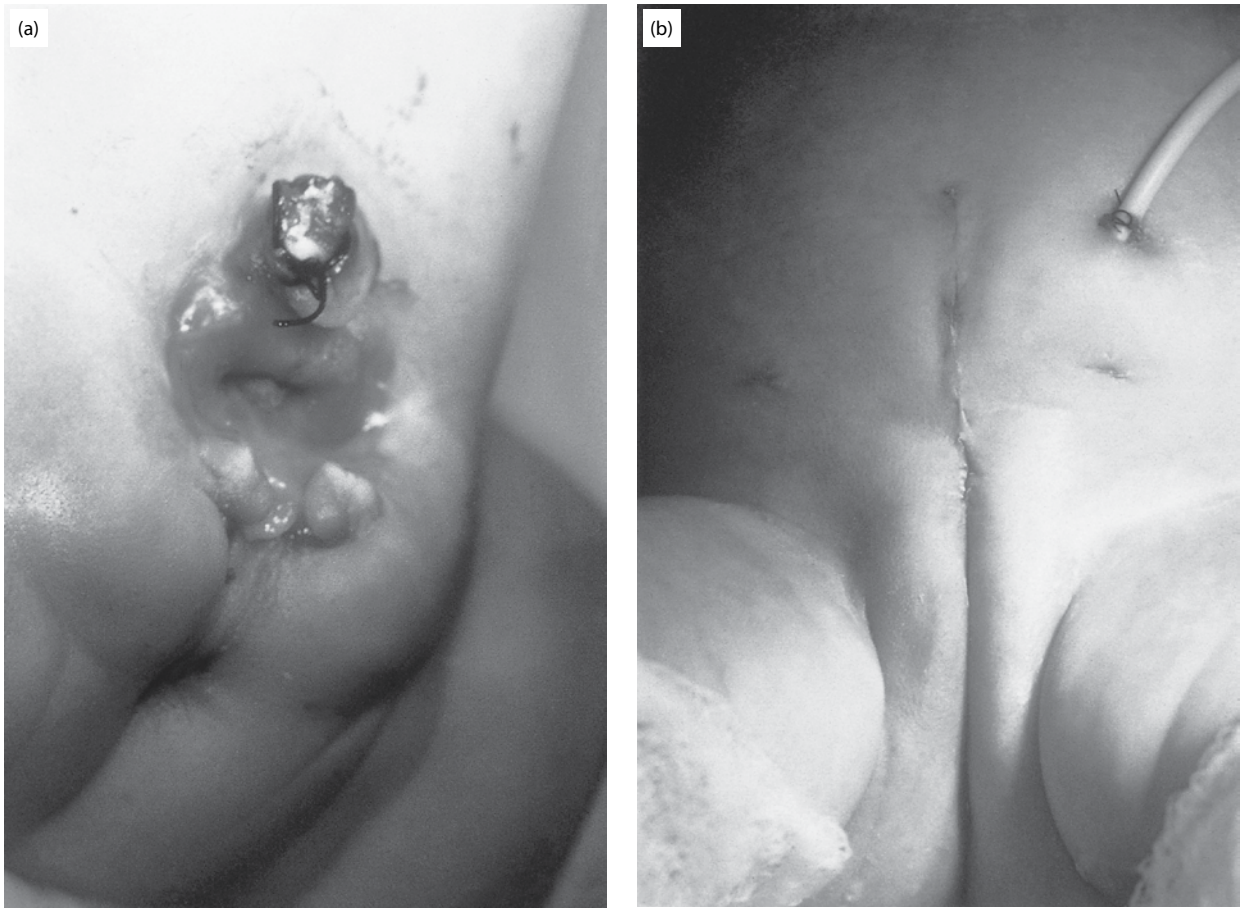


FIGURE 6.23 (a) Newborn female exstrophy patient. (b) Four weeks after initial closure.

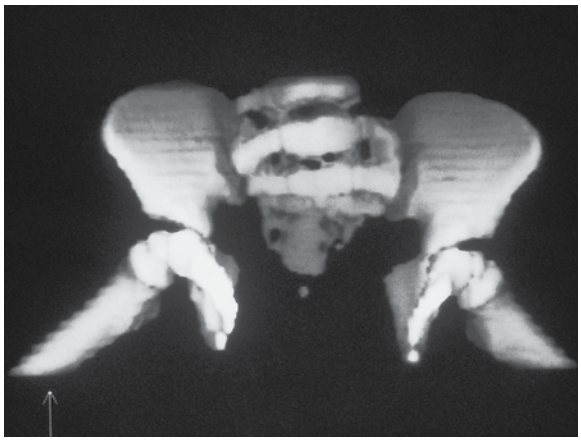


FIGURE 6.24 3-D CT reconstruction of a 5-year-old male with uncorrected classic bladder exstrophy showing a wide separation of the pubic bones and flattening of the ilial bones.

INTRAOPERATIVE CONSULTATIONS

The best approach to intraoperative consultations is to take the time to obtain a complete history. This usually is chart-based but may include talking to the parents prior to making a quick decision about a complex question. This is also the case when one is asked about a surgical finding or called to address a surgical complication. After the chart review and appropriate history, it is best to scrub into the case and review the exact location of the lesion from the skin to the region of question. One must take a fresh look at the situation and not rely totally on the primary physician. When any questions arise that deal with surgical excision of a mass, multiple radiologic modalities can be used intraoperatively, and frozen section sampling is available. *There is little to be lost in closing the patient who needs further evaluation that cannot be undertaken in the operating room, and reoperating when the problem is better understood.*

Many unusual structures may be found during a pediatric hernia repair. Among these is the finding of reproductive organs appropriate to the opposite sex. Although rare, this will usually generate an intraoperative consultation. In males, the finding of female organs, such as a fallopian tube or uterus, is termed persistent Müllerian duct syndrome or hernia uterine inguinale.[636] *The cause of this anomaly is a failure of Sertoli cell production of Müllerian inhibiting substance* (MIS), leading to feminization of pelvic structures. The testis should be undescended, but otherwise the patient is phenotypically male. Intraoperative biopsy confirms the presence of a normal testis. Testicular biopsy should be obtained from pole to pole, as opposed to the typical excisional biopsy used for infertility workup, to increase the chance of discovering an ovotestis if present.[637] Excision of the female structures should be performed with

FIGURE 6.25 Newborn with myelomeningocele.

care, avoiding injury to the adjacent functioning Wolffian duct structures. Historically, removal of the Müllerian structures was avoided by many to avoid potential injury, as there was little evidence of malignancy.[638,639] However, the routine removal of Müllerian structures, which was previously espoused by some,[640] has gained strength by an increasing number of reports of Müllerian malignancies in these patients.[641–643] Removal may be facilitated by laparoscopy.[643] In phenotypic females, the finding of male reproductive structures during hernia repair suggests androgen insensitivity syndrome. Here, the timing of excision of the male gonads is controversial: if removed early, exogenous estrogens must be administered to induce normal maturation at puberty; if left in situ until puberty, the testis must then be removed because of the high possibility of developing a gonadal tumor.[644–646] As an intraoperative consultation, it seems reasonable to remove the testis in cases of complete androgen insensitivity syndrome, especially for young infants, if a detailed discussion is conducted with the parents. However, there is little risk in leaving the testis in place and coming back later after the family has had time to make informed decisions in a less stressful environment.[646] Other investigations can be carried out during the initial intraoperative consultation after consent is obtained from the parents, including thorough physical exam, cystoscopy, vaginoscopy, and intraoperative x-ray studies.[637] Laparoscopic removal of the testis allows for a minimally invasive approach yet permits direct molecular analysis of the specimen.[647] More than 40 other tissues have been identified in and around the hernia sac. They include normal structures drawn into the sac, organ duplications as "rests," inflammatory lesions, tumors, and drainage from the abdomen into a patent processus vaginalis:[648]

1. Organs drawn into the hernia sac
   a. Appendix
   b. Bladder
   c. Gonad
   d. Meckle's diverticulum
   e. Omentum
   f. Bowel
   g. Pelvic kidney
   h. Ureter
   i. Uterus

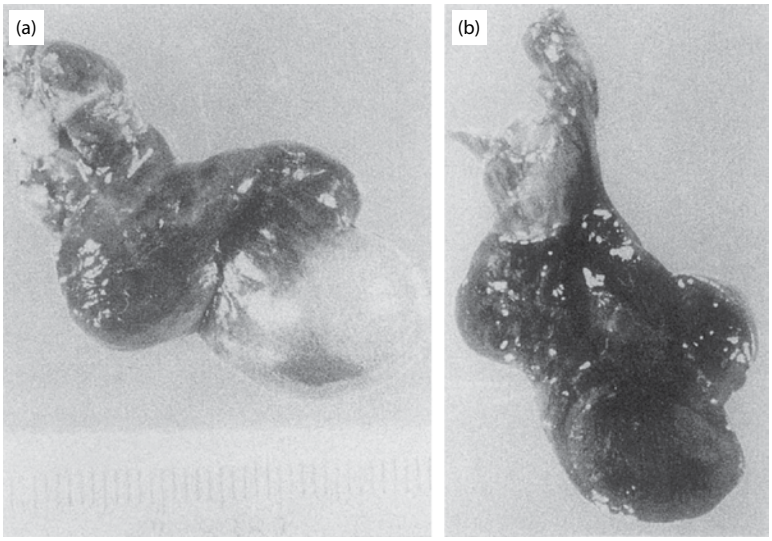


FIGURE 6.26 Infarcted testes and spermatic cord after treatment with hCG: (a) external appearance and (b) longitudinal sections. (From Sawchuk T et al. *J Urol* 1993;150:1212–13. With permission.)

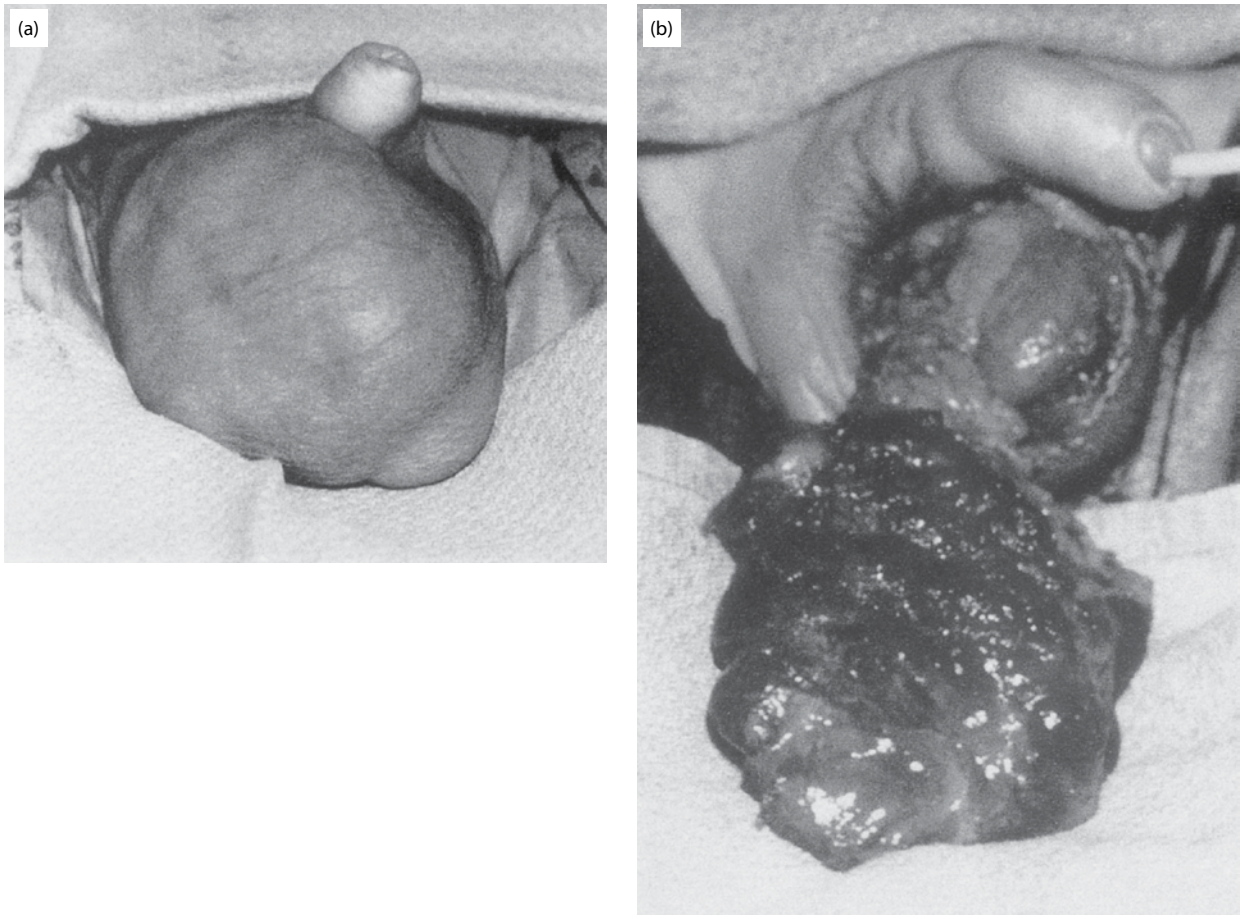


FIGURE 6.27 (a) Preoperative picture of scrotal cavernous hemangioma. (b) Intraoperative picture of a cavernous hemangioma.

2. Aberrant rests
   a. Adrenal
   b. Ectopic renal tissue
   c. Accessory spleen
3. Inflammatory lesions
   a. Abscess
   b. Funniculitis
   c. Granulomas
   d. Sarcoidosis
   e. Meconium granuloma

FIGURE 6.28 Idiopathic edema.

   f. Parasitic disease
   g. Peritonitis
   h. Polyarteritis nodosa
   i. Vasitis nodosa
   j. Xanthrogranuloma
4. Tumors and benign lesions
   a. Adrenal tumor
   b. Dermoid cyst
   c. Epidermoid cyst
   d. Epididymal cysts and nodules
   e. Calculi
   f. Hemangioma (Figure 6.27)
   g. Lymphangioma
   h. Mesenchymoma
   i. Neuroblastoma
   j. Paratesticular cyst or rhabdomyosarcoma
   k. Spermatic cord tumors
   l. Spermatocele
   m. Tunica albuginea cyst
   n. Tunica vaginalis cyst
   o. Venous thrombosis
   p. Wilms' tumor
5. Lesions that appear because of patent processus vaginalis
   a. Adrenal hemorrhage
   b. Endometriosis
   c. Meconium
   d. Blood

Unusual findings in the spermatic cord of which the urologist should be aware include those listed above, particularly ectopic adrenal tissue and accessory spleens.[649,650] In cases of ectopic adrenal tissue, the yellow color and an appearance similar to the normal gland usually aid identification. Neuroblastoma and Leydig cell tumor have also been reported to present as a mass in the spermatic cord.[651,652] In addition to the more common scrotal masses, heterotopic Wilms' tumor and neuroblastoma have been reported.[637] Both adrenal and splenic tissue have also been found in the scrotum, and splenogonadal fusion is not uncommon with an undescended left testis. Excision of these masses is usually best, with careful pathologic evaluation to confirm the diagnosis. In the rare event that exploration through a scrotal incision (i.e., for possible torsion) reveals a testicular mass, a separate inguinal incision should be made and radical orchiectomy performed at the internal ring. One should at least widely excise the scrotal incision site if the testicle remains intact or perform hemiscrotectomy if there is concern for contamination of the incision or after any percutaneous biopsy revealing a testicular neoplasm.[637,653]

Vasal abnormalities noted during surgery (i.e., the absence of the vas with normal testicle) should result in imaging workup postoperatively with ultrasound to assess for upper tract abnormalities, such as renal agenesis or ectopia, which have been associated with the absence of the vas.[654,655] Based on examination of pathologic specimens, the estimated risk of injury to the vas or epididymis during pediatric hernia repair is approximately 0.5%,[656] although most are probably not recognized until later in life during evaluation for infertility. Vasal injury that is identified during pediatric hernia repair mandates intraoperative

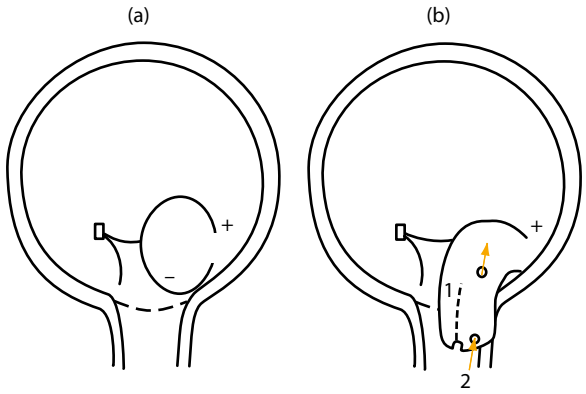
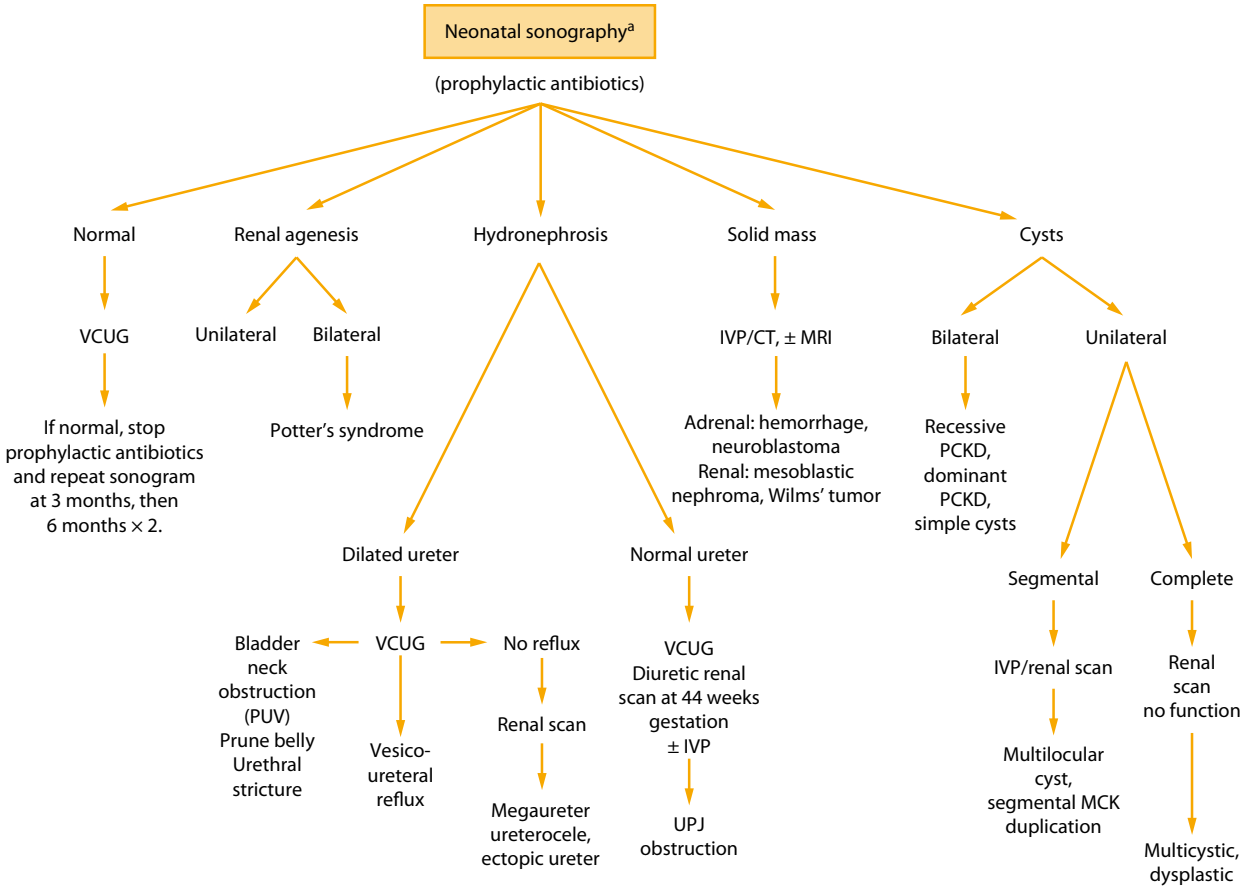


FIGURE 6.30 Technique for incision of ureteroceles. (a) Incision for an intravesical ureterocele. (b) Techniques for an ectopic ureterocele: (1) incising proximally and (2) puncturing urethral and intravesical segments separately. (From Blyth B et al. *J Urol* 1993;149:556–60. With permission.)

FIGURE 6.29 Severely androgenized patient with CAH.



[a](1) Unilateral hydronephrotic and cystic lesions can be evaluated as an outpatient.
(2) Bilateral lesions should be evaluated prior to discharge.
(3) Masses should be evaluated prior to discharge.

FIGURE 6.31 Postnatal flow diagram. PCKD, polycystic kidney disease.

pediatric urologic consultation. Previous studies have documented the ease with which vasal trauma may occur secondary to intraoperative manipulation.[657] In cases of transection, immediate microsurgical repair is indicated, although this may be technically challenging in prepubertal boys.[658,659] Crush injuries may result in future obstruction. In these situations, the decision regarding treatment must be individualized. In most instances, observation is indicated. However, when a severe crush injury has occurred, as when a clamp is applied and closed with obvious injury, excision and primary reanastomosis are indicated.

Intraoperative consultations relating to the bladder are usually a result of trauma or iatrogenic injury during surgery. Intraoperative injury to the bladder is rare but may occur secondary to percutaneous laparoscopic procedures or during inguinal hernia repair. When it happens, it is best managed by primary closure, and bladder drainage in the postoperative period via a urethral catheter and/or suprapubic tube. Perivesical drainage is also appropriate in the immediate postoperative period. A cystogram to confirm the absence of extravasation should be performed prior to removal of drainage catheters. Rarely, during umbilical hernia repair, an urachal abnormality is discovered. In these cases, the urachus should be traced to the dome of the bladder and excised with primary closure of the bladder.[637] If the diagnosis is uncertain, an intraoperative cystogram may clarify the picture. Later, evaluation for other associated genitourinary abnormalities, which may be seen in approximately 35% of cases, is warranted.[660]

Most consultations related to the kidney or ureter occur in patients with renal trauma. As in other forms of renal trauma, there has been a movement toward nonoperative management of pediatric renal injuries, including those identified intraoperatively.[661] When called in for an intraoperative evaluation of a renal trauma, it is important to obtain at least a single-shot IVP (2 mL/kg IV bolus) to document the presence and function of the contralateral kidney if no preoperative imaging exists.[662] This may also aid in staging the renal trauma, especially if a three-phase IVP can be obtained. When an expanding retroperitoneal mass is explored after trauma, early renal vascular control should be the main objective to help prevent unnecessary nephrectomy. Selective angioembolization can play a role in specific cases of isolated segmental bleeding, but has limitations.[662] When appropriate steps are taken, the vast majority of kidneys can be saved after renal injuries.

Traumatic separation of the ureter and pelvis occasionally occurs in children. Unlike many injuries where drainage and observation is indicated, complete avulsion of the

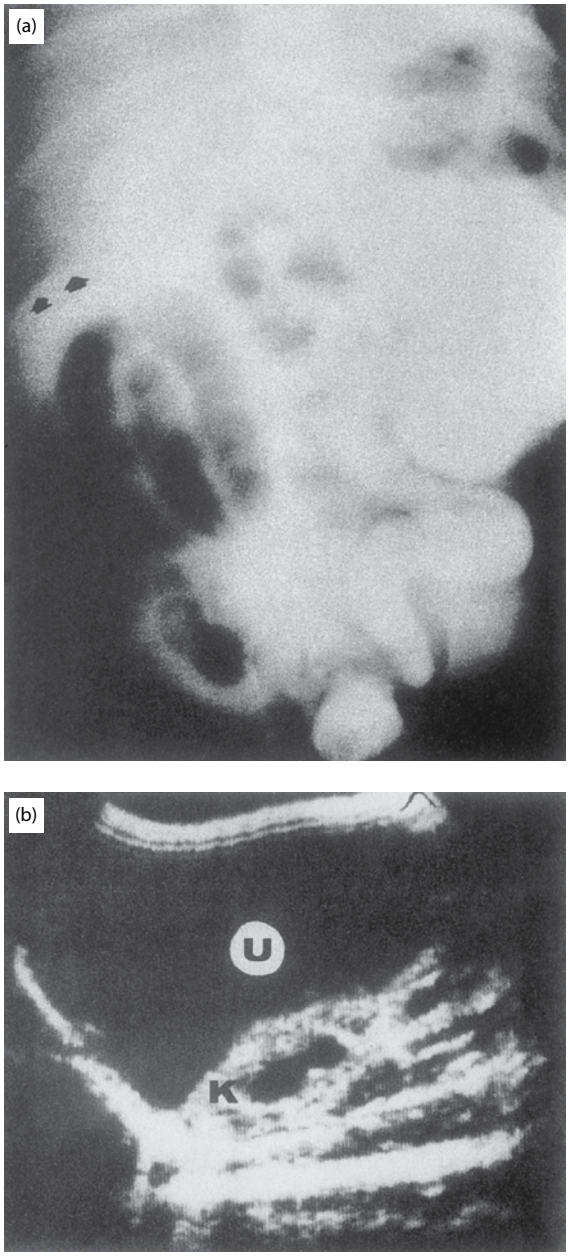


FIGURE 6.32 (a) Voiding cystourethrogram of urinary ascites. The black arrows point to the liver edge. (b) Ultrasound study showing a retroperitoneal urinoma. K, kidney; U, urine collection. (From Rittenberg M. et al. *J Urol* 1988;140:993–6. With permission.)

ureter should be surgically repaired as quickly as possible. It is a more complex procedure than a standard UPJ repair because the pelvis is almost always intrarenal and mobilization of the kidney and ureter to prevent tension on the anastomosis can be difficult. The procedure is much more difficult if the correction is delayed because of edema with subsequent scar formation. However, when called to evaluate a dilated or otherwise abnormal ureter, injured or not, temporary drainage by a percutaneous nephrostomy tube or ureterostomy may be the best course to allow accurate determination of the etiology of the abnormality before proceeding with reconstruction.[637]

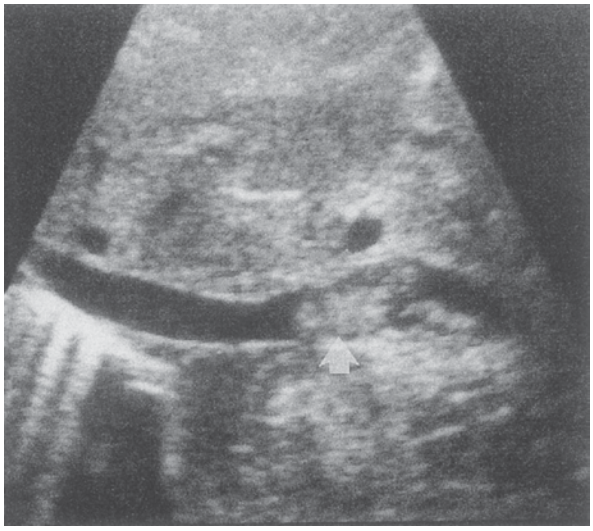


FIGURE 6.33 RVT. Ultrasound through the inferior vena cava (IVC) showing thrombus within the IVC at the level of the renal vein. (From Hibbert J et al. *Br J Radiol* 1997;70:1191–4. With permission.)

As a result of advances in imaging and thorough preoperative evaluations, consultations because of a previously undiagnosed renal mass, formerly common, are now unusual. One must consider the same differential for cystic masses as discussed earlier. Often, a dilated renal pelvis may be mistaken for a cystic mass. A solid mass is most likely a Wilms' tumor when outside of the newborn period, but other possibilities exist. Occasionally, an ectopic or a pelvic kidney may be confused with a pelvic mass and necessitate an intraoperative consultation. Reports of inadvertent nephrectomy in patients with solitary ectopic kidneys are found in the literature.[637] When it is unclear whether the mass in question is a solitary kidney, intraoperative imaging may be necessary to clarify the situation. This is critical, as reports indicate that up to 10% of all pelvic kidneys are solitary.[663] Intraoperatively, it is important to remember that ectopic kidneys may not be reniform in shape and tend to have an anomalous blood supply derived from the aorta and iliac vessels, or the superior mesenteric artery.[663] Simple needle aspiration to confirm the presence of urine may also be useful in identifying a kidney. Fusion anomalies and horseshoe kidneys may also be a source of confusion and prompt urologic consultation.

Use of laparoscopy and robotic surgery continues to increase in pediatric and adult surgery in all specialties. Intraopertive issues unique to minimally invasive techniques include port placement injuries and the decision of whether to convert to open surgery when consulted. Veress needle or port placement injury to urologic organs is rare, with bowel and blood vessel injuries being more common.[664] The bladder is the most common urologic organ inured by port or Veress needle placement,[409,665] and the more superior location of the bladder in children makes care all the more important. Actively draining the bladder by aspiration via a catheter can help to ensure it is as empty as possible. Injury to any urologic organ during surgery may go unrecognized due to the limited field of vision inherent in laparoscopic surgery. A large meta-analysis found that nearly half

of bladder injuries were missed at the time of laparoscopic surgery.[666] When an injury is recognized, the same general principles apply to a given injury as with open surgery. Nearly any repair can be accomplished laparoscopically or robotically if the surgeon is experienced, thus avoiding the need to convert to open surgery.[666,667] However, as with any intraoperative consultation, one must step back and do everything possible to ensure the best outcome. If conversion to open surgery is needed to fully gain access to or remedy the problem, it should be done.

Occasionally, the urologist will be called on to evaluate an infant for difficulty in placing a urethral catheter. Initially, properly lubricating the urethra by injecting 2% lidocaine jelly facilitates catheter insertion. Most commonly, these will be male neonates who have had multiple attempts at catheterization before urologic consultation. In these cases, a good option may be to use a curved-tip "coude" catheter, which has recently become available in pediatric sizes. When these are not available, or will not pass, a small catheter guide may be placed within a pediatric feeding tube and manipulated into the bladder. If no guides are available, bending a heavy wire suture for use as a catheter guide may be successful.[668,669] Lubricating jelly must be placed on the guide to facilitate its removal. In cases where this fails, proceeding directly to cystoscopy to evaluate the possibility of a false passage is warranted. Use of a guidewire placed under direct vision, followed by catheter placement over the wire, ensures proper catheter placement. If council tip catheters are not available in pediatric sizes, standard catheters can be modified to pass over a wire. One must be extremely careful if cutting off the tip transversely to avoid damaging the balloon. This is especially difficult on pediatric-sized catheters. Other techniques include a longitudinal cut[670] or the Blitz technique,[671] which uses an 18-gauge angiocath to guide the wire directly through the tip of a catheter. The balloon should be tested prior to insertion of any catheter that has been altered, and the alteration should be documented so there is no concern for breakage when the Foley is removed. Special precautions should be considered when needing to perform cystoscopy or other urinary tract manipulations on patients with spinal cord injuries: (1) the possibility of autonomic dysflexia for lesions at T6 or higher, (2) an increased risk of infection warranting antibiotic coverage when there is trauma or dilation of the urinary tract, and (3) the possibility that the wire may double back over itself in a small-capacity bladder, leading to placement of the Foley balloon in the urethra.[672] When the bladder is palpable, a percutaneous cystotomy may be performed under local anesthesia or in the operating room. Alternatively, a large-gauge needle placed into the distended bladder will permit insertion of a guidewire, dilation of the tract, and placement of a suprapubic catheter.

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CHAPTER 7

Urinary Tract Infections in Children

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INTRODUCTION

Advances in research have enabled us to better understand the etiology and pathophysiology of urinary tract infections (UTIs) in children, which in turn has further refined diagnostic and treatment algorithms, and the management of long-term sequelae. The role of bacterial virulence in the etiology of UTIs has assumed greater importance since it has been recognized that bacteria are genetically encoded to invade the urinary tract, evade detection by the innate immune system, and cause tissue injury. Interacting with these virulence factors are a multitude of host defense factors operating at every level of the urinary tract. Collectively, these complex host–parasite interactions determine an individual's predisposition to urinary infection.

Epidemiology

UTIs in children may be symptomatic or asymptomatic. Symptomatic infections may be confined to the bladder (cystitis), or they may involve the upper collecting system (ureteritis and pyelitis) or extend into the renal parenchyma (pyelonephritis). Age, gender, race, circumcision status, the method of detection, and presentation all influence the prevalence of symptomatic versus asymptomatic urinary infection. With 174 per 100,000 infants younger than 3 months being hospitalized each year for UTIs, it has been estimated that the annual cost to the U.S. healthcare system for hospitalization for UTI approaches $180 million.[1]

Historically, the incidence of neonatal bacteriuria has been reported as 1%–1.4%, with males predominating.[2–4] However, the actual incidence during infancy has probably been underestimated in the past, partly because of the difficulty in diagnosing UTI in this age group. In a 3-year prospective study of 3581 infants (aged 0–1 year) in Goteborg, Sweden, asymptomatic bacteriuria (ABU) was confirmed by suprapubic aspiration (SPA) of urine in 2.5% of boys and 0.9% of girls.[5] Symptomatic urinary infection occurred equally often in both sexes (1.2% of boys and 1.1% of girls). Overall, 3.7% of boys and 2% of girls had positive urine cultures during the first year of life. The male predominance noted in the Goteborg study during the first few months of life has also been reported by others.[6–9] Uncircumcised infant boys are 8–10 times more likely to have symptomatic urinary infection than their circumcised counterparts.[10]

During preschool and school age, the male-to-female ratio observed in neonates is reversed, making screening bacteriuria more prevalent in girls (Table 7.1).[8,9] In several large studies of school-aged children, the aggregate risk of screening bacteriuria has been reported to be 0.7%–1.95% of girls and 0.04%–0.2% of boys.[11–15] However, in as many as one-third of these children a prior history of UTI or voiding symptoms could be elicited (Table 7.2). Based on an average annual incidence figure of 0.4%, Kunin (1964) estimated that bacteriuria will develop in approximately 5% of girls prior to graduation from high school. Additional data collected by Kunin (1970) revealed that infection will recur in up to 80% of all school-aged white girls and 60% of black girls within 5 years.[11] It must also be considered that UTIs may be underdiagnosed in children thought to have infections from other sources. O'Brien et al. reported that 4% of children less than 5 years of age who were seen in primary care settings for acute illness met the criteria for UTI ($>10^5$ organisms) despite having alternate site infections.[16]

In a prospective population-based study of symptomatic UTIs in children living in Goteborg, Sweden, Winberg et al. estimated that the aggregate risk for symptomatic UTI up to age 11 was at least 3% for girls and 1.1% for boys.[17] In an update of a previous study, the incidence of culture-documented UTIs was twice as high as previously estimated, affecting 7.8% of girls and 1.6% of boys during the first 6 years of life.[18] To confirm these findings, Mårild and Jodal performed a retrospective population-based study of 41,000 children of Goteborg, Sweden.[19] The cumulative incidence rate of symptomatic UTIs was 6.6% for girls and 1.8% for boys. Pooled prevalence rates of UTI in febrile females ages 0–3, 3–6, 6–12, and >12 months was 7.5%, 5.7%, 8.3%, and 2.1%, respectively. Among febrile males ages 0–3 months old, the prevalence rates of UTI were 2.4% of those circumcised and 20.1% of those uncircumcised.[20] These data probably do not reflect an increasing incidence of UTIs since the publication of the earlier reports, but instead a greater detection rate. In all these epidemiologic studies, the incidence of febrile UTIs was greatest in infant boys and girls compared with children over 2 years of age. Gender differences in the incidence rates of first-time febrile and nonfebrile UTIs were most evident in children greater than 2 years old. Girls greater than 2 years old were much more likely to present with first-time UTI, both with and without fever, compared with their age-matched male counterparts (Table 7.3) (Figure 7.1a and b).

Once treated, infants with symptomatic urinary infections are at risk for recurrent infection (26%), usually in the first 3 months of follow-up. In older girls, the risk for

TABLE 7.1 Gender ratio of urinary tract infections

	Females	Males
Neonate	0.4	1
1–6 months	1.5	1
6–12 months	4.0	1
1–3 years	10.0	1
3–11 years	9.0	1
11–16 years	2.0	1

Source: Belman AB, Kaplan GW. *Genitourinary Problems in Pediatrics*, W.B. Saunders Co., Philadelphia, 1981; Winberg J et al. *Acta Paediatr Scand* 1974;252(suppl.):1.

TABLE 7.2 Clinical history and symptoms of 109 children with "screening" bacteriuria

History/symptoms	Percent
All symptoms (excluding nocturnal enuresis)	70
Urgency	54
Frequency	53
Nocturnal enuresis	51
Diurnal enuresis	47
Previous UTI	20
Dysuria	13
Unexplained fever	7
Flank pain	4
Nocturia	4

Source: Savage DCL et al. *Arch Dis Child* 1973;48:8.

recurrence following symptomatic urinary infection is as high as 40%–60% within 18 months. This risk persists into adulthood.[8] In one study, 60 girls with childhood bacteriuria followed into adulthood (9- to 18-year follow-up) were compared with 38 nonbacteriuric controls.[21] During pregnancy, a significantly greater incidence of bacteriuria was diagnosed in the group with the history of positive urine cultures in childhood (63.8%) than in the controls (26.7%). Further evidence supporting a lifelong risk for symptomatic urinary infection in individuals presenting during childhood is reported by the Goteborg Childhood UTI Research Group. These authors followed 111 women with renal scarring or recurrent UTIs from their first UTI until adulthood, with a median follow-up time of 15 years. Febrile UTIs were more prevalent than nonfebrile UTIs during the first 10 years of life but continued to occur into the third decade. Although the prevalence of febrile UTIs diminished in adulthood, women with renal scarring during childhood were significantly more likely to have subsequent febrile UTIs. Overall, the median incidence of symptomatic UTIs was seven per individual.[22,23] As detailed later in the chapter, vesicoureteral reflux (VUR) increases susceptibility to acute pyelonephritis (APN) and perhaps even increases the risk for UTI, but only when the severity of VUR is so great that it promotes urinary stasis.

Evidence that heredity plays a role in determining individual susceptibility to UTI is accumulating. Family members of children prone to APN are reported to have a 15% incidence of APN, compared with only 3% of relatives of control subjects.[24] The daughters of mothers who had been bacteriuric in childhood show a higher incidence of UTI, and female siblings also tend to show a higher incidence of bacteriuria.[21,25] Children with first-time pyelonephritis significantly more often have relatives with a history of UTI than do controls.[26] Racially dependent differences in the prevalence of UTIs and in the rate of bacteriuria have also been reported. Kunin et al. (1964) reported a 1.2% bacteriuria prevalence rate in white girls versus a rate of 0.5% in black girls in the same age group. In a retrospective review, the number of black girls evaluated following UTI who were found to have VUR was one-third that of white girls at an institution where an equal number of black and white girls were hospitalized.[27] This observation was subsequently confirmed by a prospective study of patients admitted to this same institution with febrile UTIs.[7] Experimental UTI in mice is also significantly influenced by heredity, as evidenced by a slower response to treatment in certain strains of inbred mice compared with others that resolve the UTI more rapidly.[28] These same studies have also demonstrated that the acute inflammation and acquired immune response (antibody production) that follow urinary infection differ among genetically different strains of mice. As stated, "[this] result strongly suggests that the presence or absence of specific host genes will determine how effectively an *E. coli* UTI will be resolved."

There are likely genetic components that contribute to UTI susceptibility. While mice lacking the interleukin 8 (IL-8) receptor are more susceptible to APN than their wild-type counterparts, a similar increased risk for APN is seen in children with diminished chemokine receptor 1 (CXCR1) expression, which is homologous to the murine IL-8 receptor.[24]

There are also other groups of patients who are at higher risk for UTI-related morbidity and/or mortality. Specific examples include a higher risk for recurrent pyelonephritis, bacteremia, and allograph dysfunction in renal transplant patients who contract UTI within the first 3 months of transplantation. In spinal cord injury patients, the second most common cause of death is UTI.[29,30] Catheter-associated UTI is the most common nosocomial infection in hospitals in the United States and nursing homes, with an estimated aggregate cost of more than $600 million to our healthcare system.[31,32]

Bacteriology

Research has identified specific virulence factors that determine an organism's pathogenic potential, thus differentiating strains commonly associated with ABU, cystitis, or APN. Not all strains are capable of causing UTI. Uropathogenic *Escherichia coli* (UPEC) are specific subsets of extraintestinal pathogenic *E. coli* that possess specific virulence properties. Virulence factors that lead to infection include bacterial adherence, toxin production, motility, metal acquisition capacity, and the ability to evade host defenses.[33]

TABLE 7.3 Prevalence of UTI in girls <2 years old and boys <1 year old with respect to common demographic and clinical indicators

	N	Prevalence % (95% CI)	*p* Value
Overall	2411	3.3 (2.6–4.0)	
Demographics			
Sex			**<0.001**
Girls	1469	4.3 (3.3–5.3)	
Boys	942	1.8 (1.0–2.6)	
Race			**<0.001**
White	291	10.7 (7.1–14.3)	
African American	2014	2.1 (1.5–2.7)	
Other	106	5.7 (1.3–10.1)	
Sex/Race			
Girls			**<0.001**
White	174	16.1 (10.6–21.6)	
Nonwhite	1295	2.7 (1.9-3.7)	
Boys			0.52
White	117	2.6 (0.5–7.3)	
Nonwhite	825	1.7 (0.9–2.8)	
Age/Sex			
Boys			0.14
<6 months	391	2.7 (1.2–4.7)	
>6 months	551	1.3 (0.5–2.6)	
Girls			**<0.001**
<12 months	813	6.0 (4.5–7.9)	
>12 months	656	2.1 (1.2–3.6)	
Another potential source of fever present			
Yes	1858	2.7 (2.0–3.4)	**<0.001**
No	474	5.9 (3.8–8.0)	
Circumcision status			**<0.002**
Yes	497	1.2 (0.2–2.2)	
No	75	8.0 (1.9–14.1)	
Temperature			**<0.003**
>39°C	1623	3.9 (3.0–4.8)	
<39°C	788	2.2 (1.2–3.2)	
General appearance			**<0.001**
Ill	681	5.7 (4.0–7.4)	
Well	1650	2.4 (1.7–3.1)	

Source: Shaw K et al. *Pediatrics* 1999;102(2):e16–22.
Note: Indicators in boldface type correlated significantly with the likelihood of diagnosing a UTI.
Abbreviation: CI, confidence interval.

A large family of gram-negative, aerobic bacilli known as Enterobacteriaciae cause the majority of uncomplicated UTIs. Included in this family are the species *Escherichia*, *Klebsiella*, *Enterobacter*, *Citrobacter*, *Proteus*, *Providencia*, *Morganella*, *Serratia*, and *Salmonella*. Of these, *E. coli* is by far the most frequently isolated organism, being responsible for approximately 80% of UTIs. This family of bacteria is generally characterized by a negative reaction to the oxidase test and the capacity to ferment glucose and reduce nitrates to nitrite. *Pseudomonas* is also a gram-negative, aerobic bacillus but is distinct and unrelated to Enterobacteriaciae. Most *Pseudomonas* recovered from the urine are of relatively low virulence and do not tend to invade tissue unless host defense mechanisms are compromised.

The most common gram-positive organisms found in UTIs are *Staphylococcus* and *Enterococcus*. Anaerobic

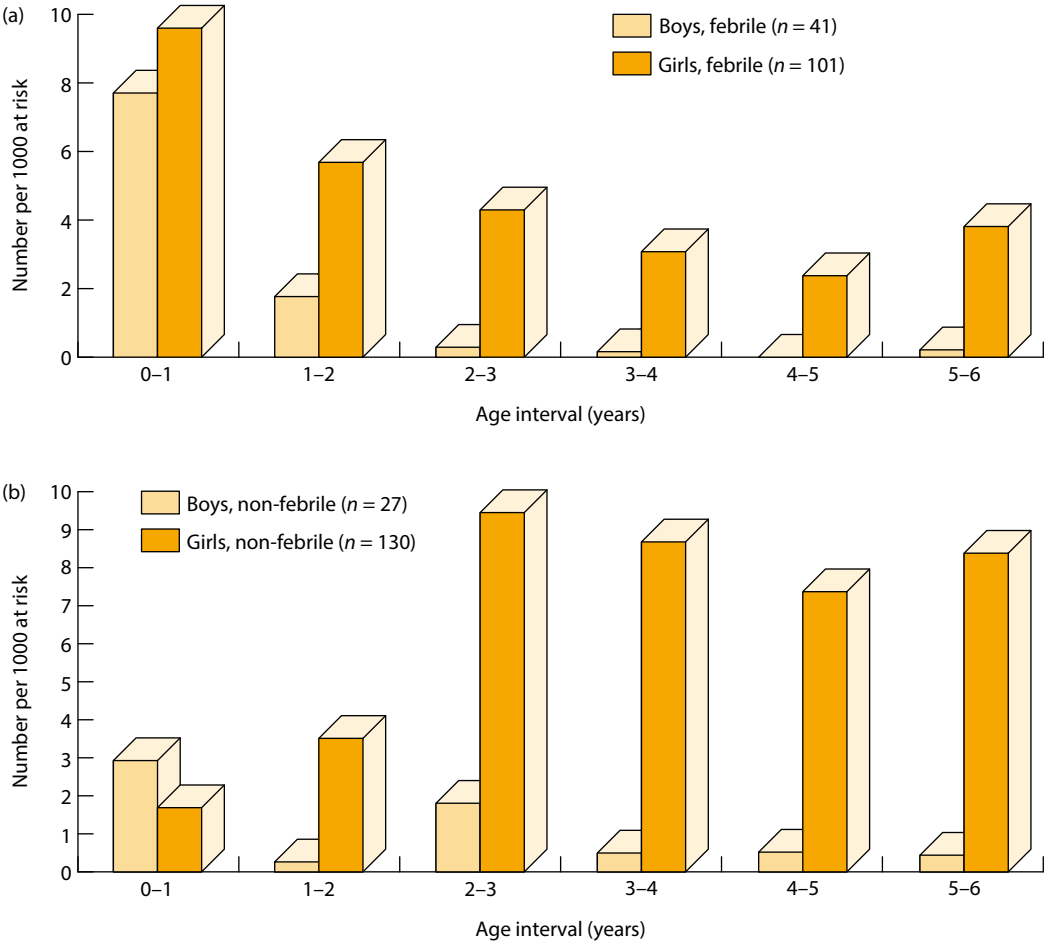

FIGURE 7.1 (a) Annual incidence rate in 1-year intervals of febrile UTI in children studied during a 20-month period between 1979 and 1981. (b) Annual incidence rate in 1-year intervals of nonfebrile UTI in children studied during a 20-month period between 1979 and 1981. (Adapted from Mårild S, Jodal U. *Acta Paediatr* 1998;87:549–52.)

fecal flora rarely produce UTIs despite being 100–1000 times more abundant than *E. coli* in stool.[34] Occasionally, unusual or fastidious organisms may produce infections that are difficult to detect because they do not grow well in commonly used culture media. For example, *Haemophilus influenzae* has been reported to cause urinary infections, as well as epididymo-orchitis in infant males.[35,36] Other unusual organisms include *Salmonella* sp. and *Shigella*. Although lactobacilli, corynebacteria, and α-*Streptococcus* may rarely cause UTI, they probably should be considered contaminants unless they are found in the culture of specimens obtained by SPA or catheterization.

The bacteriological findings in the Goteborg study suggest that "the [predisposing] environmental conditions in the periurethral region and the host defense mechanisms vary with age and sex."[17] This study identified four characteristic bacteriologic trends in childhood UTIs:

1. A high frequency of *Proteus* sp. infections in older boys (most of whom were uncircumcised), and greater variability in infecting organisms in boys than in girls
2. A greater likelihood of staphylococcal infection in adolescence, especially in girls
3. A greater frequency of *E. coli* urinary infection in neonatal boys than in girls of that age
4. A decreased frequency of *Klebsiella* urinary infection in older children (Table 7.4)

Other general rules include the fact that the majority of uncomplicated infections are caused by a single organism. Patients with complicated infections, particularly those children who have been managed with long-term catheterization, may have multiple organisms. Sometimes the strain of bacterium is suggestive of underlying urinary pathology, such as the relationship of *Proteus* sp. and struvite stones.

Serology

E. coli, the most common species of uropathogens, can be typed serologically by three major groups of antigenic structures capable of producing specific antibodies. There are more than 150 O (cell wall) antigens, more than 50 H (flagellar) antigens, and approximately 100 K (capsular) antigens. Not all strains are typable. Serological classification in UTI is restricted mainly to O antigens. Early studies have attempted to correlate serological markers with increased virulence or tissue invasiveness. Most of these were epidemiological studies that were conducted prior

TABLE 7.4 Infecting bacteria (percent) isolated from "first-time" urinary infection in children categorized by age and gender

		Females (%)		Males[b] (%)	
Infecting Organism	**All Neonates ($n = 73$)**	**1 month– 10 years[a] ($n = 30$)**	**10–16 years ($n = 30$)**	**1 month–10 years ($n = 62$)**	**10–16 years ($n = 42$)**
E. coli	**57% (females) 83% (males)**	**83%**	**60%**	**85%**	**33%**
Klebsiella	11	4	0	2	2
Proteus sp.	0	3	0	5	**33**
Enterococcus	3	2	0	0	2
Staphylococcus	1	4	**30**	0	12
Other, mixed, or unknown	9	11	10	8	17

Source: Winberg J et al. *Acta Paediatr Scand* 1974;252(Suppl.):1.
[a] No difference between girls 1 month to 1 year old and 1–10 years old.
[b] Males are not routinely circumcised in Scandinavia.

to discovery of the special role of specific virulence factors, such as adhesins (attachment structures). In contrast to patients with cystitis or ABU, patients with pyelonephritis have been found to be more frequently infected with certain O typable strains and strains having certain K antigens. Eight O antigen types (O1, O2, O4, O6, O7, O18, O25, and O75) were the cause of 80% of cases of pyelonephritis in one report. Another study reported that *E. coli* possessing five K antigens (K1, K2, K3, K12, and K13) accounted for 70% of isolates from patients with pyelonephritis.[37] These earlier serologic studies have been extended to identify more specific O:K:H combination serotypes characteristic of pyelonephritogenic strains. However, specific attachment structures appear to be the more important determinants of disease severity and of the likelihood of postpyelonephritic renal scarring.

Bacterial Virulence Factors

The term *virulence* simply refers to the ability of microorganisms to cause disease. The concept of uropathogenic bacteria refers to certain strains that are selected from the fecal flora, not by chance or prevalence, but because of the presence of specific virulence factors that enhance colonization of the uroepithelium. Other virulence factors aid in the persistence of bacteria in the urinary tract and provide these organisms with the capacity to induce inflammation of the urethra, bladder, or renal parenchyma. The following information will include known data detailing specific *E. coli* virulence factors. Advancements in technology continually increase our knowledge of how bacteria propagate and survive.[38]

Adherence

Bacterial adherence or attachment is an essential initiating step in all infections. Perineal colonization by uropathogenic bacteria has been found to precede clinical UTI in women and children at risk for UTI.[6,39–42] Tissue invasion, inflammation, and cell damage are secondary events. Utilizing specialized structures (adhesins), uropathogenic bacteria, especially *E. coli*, can attach to specific receptor sites on the uroepithelium and can also bind in a nonspecific manner by electrostatic and hydrophobic factors. By virtue of such attachment, virulent strains of bacteria can ascend into the upper urinary tract even in the absence of structural abnormalities, such as VUR.

Specific attachment (bacterial tropism) to uroepithelial cells is mediated by adhesins localized either in an outer coat of capsule or on specialized structures. Fimbrial gene clusters (type 1, P, F1c, Dr, Auf, S, and M) or operons encode all the genes necessary for fimbriae assembly.[33] Collectively known as fimbria, these attachment structures are capable of recognizing and attaching to receptors located on uroepithelial cells and to some constituents of the basement membrane. Type 1 fimbria mediates agglutination between bacteria and cells in culture. Since this agglutination can be competitively inhibited by a mannose-rich solution, these fimbriae are therefore termed mannose sensitive. Other fimbriae attach to uroepithelial cells in the presence of soluble mannose and are termed mannose resistant (Figure 7.2). Uropathogenic bacteria rely on both mannose-sensitive type 1 fimbria and mannose-resistant type 2 fimbria (also termed P-fimbria) to colonize the urinary tract. In addition to type 1 and P-fimbria, uropathogenic bacteria employ several other adhesins, both fimbrial and nonfimbrial. Unfortunately, little epidemiological evidence exists that clarifies the role of these additional adhesins on *E. coli* (S-fimbria, FIC-fimbria, and S/FIC-related fimbria), *Klebsiella* (MR/K HA), and *Proteus* sp. (MR/P HA, PMF, ATF, NAF, and UCA) in the pathogenesis of UTI.

In addition to promoting attachment, type 1 fimbriae mediate bacterial invasion into the uroepithelial cells themselves, thus protecting bacteria from antibiotics that do not penetrate the cell's membrane, such as aminoglycosides.[43] In fact, viable internalized bacteria can be isolated from uroepithelial cells 48 hours after infection, and may account for recurrent infection by the same bacterial strain (Figure 7.3). Once type 1–fimbriated *E. coli* attach, the uroepithelial cells undergo apoptosis (programmed cell death) that results in bladder mucosal ulceration.

Although the entire urothelial surface, including the upper urinary tract, contains glycoprotein receptors for type 1 fimbria, no evidence exists that implicates type 1 fimbria directly in the pathogenesis of pyelonephritis. However, it

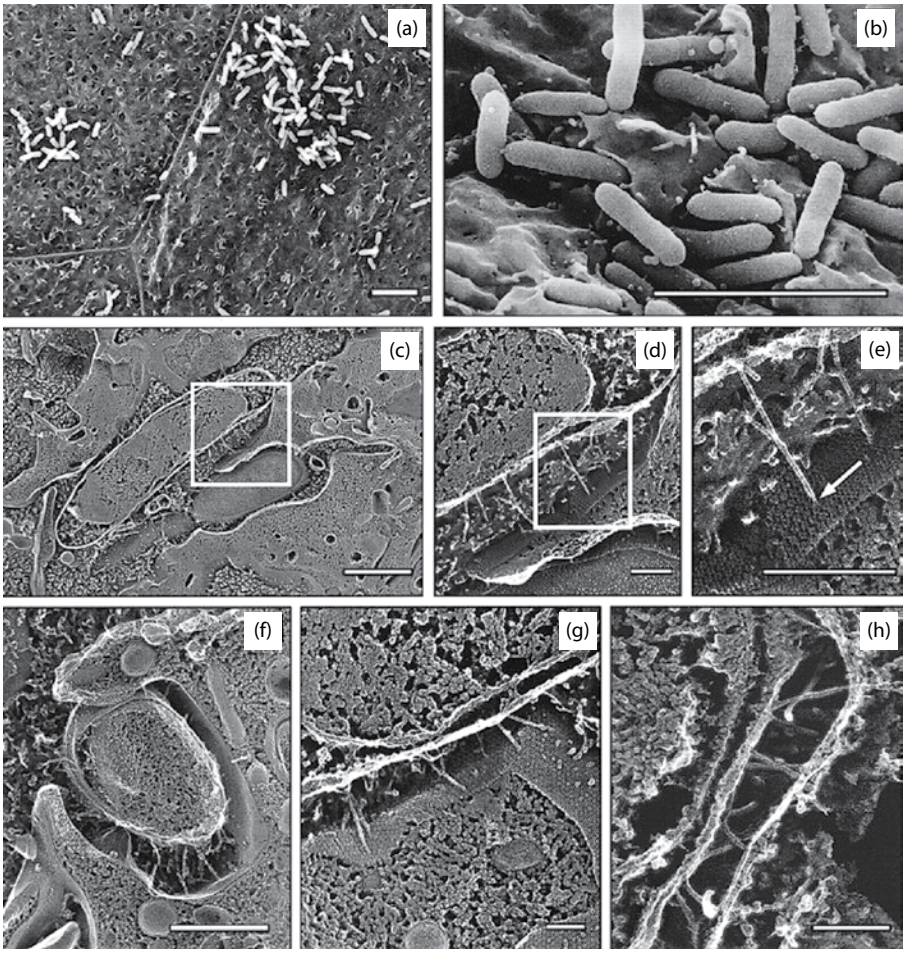

FIGURE 7.2 Type 1 pilus-mediated bacterial adherence to the bladder epithelium. Mouse bladders were processed for (a, b) scanning electron microscopy (SEM) and high-resolution EM at 2 h after infection with *E. coli* NU14. The boxed areas in (c) and (d) are shown magnified in (d) and (e), respectively. The arrow in (e) indicates the FimH-containing tip. In (h), type 1 pili span from the host cell membrane on the right to the bacterium on the left. Scale bars = 5 μm (a, b), 0.5 μm (c, f), and 0.1 μm (d–h). (From Mulvey MA et al. *Science* 1998;282:1494–7.)

has been demonstrated in experimental models and clinical studies that once pyelonephritis occurs, the presence of type 1 fimbria significantly increases a strain's ability to persist in the urinary tract and to stimulate inflammation.[44–46]

Clinical and experimental studies have shown that pyelonephritic *E. coli* frequently possess fimbriae that can recognize and agglutinate erythrocytes of the P1-blood group. Hence, this type of pili has been termed P-fimbria. The P-fimbriae are mannose-resistant adhesins that attach to the carbohydrate portion (α-D-galactopyranosyl-(1–4)-β-D-galactopyranoside) of the glycolipid antigen in the P-blood group series, which is also expressed by human uroepithelial cells.[47,48] The components of P-fimbria are encoded by 11 genes in the pap gene cluster, of which pap E, F, and G encode for the adhesin subunits.

Further research has identified that not all P-fimbriae are alike. Proteins located at the tip (G-tip proteins, or tip adhesins) determine the fimbria's specific attachment properties. Three classes have been identified, of which only class II and class III P-fimbriae have uropathogenic potential. In vitro studies have found that the class III P-fimbriae bind receptors found in higher density on bladder uroepithelium. In contrast, class II tip adhesins may be more important in the evolution of APN by virtue of an increased density of class II–specific receptors located on the uroepithelium of the upper urinary tract.[49] Roberts et al. have recently described a statistically significant greater likelihood of clinical and histologic indicators of APN in primates inoculated with class II–fimbriated *E. coli* than when primates are inoculated with class III–fimbriated *E. coli*.[50]

Epidemiological studies in children have provided considerable evidence that the presence of P-fimbriae on *E. coli* is a significant virulence factor, particularly in upper UTIs. These studies have shown that 76%–94% of pyelonephritogenic strains of *E. coli* are P-fimbriated compared with 19%–23% of cystitis strains, 14%–18% of strains isolated from patients with ABU, and 7%–16% of fecal isolate strains.[38,51] Other evidence supporting the importance of P-fimbria in causing upper UTIs comes from animal model studies. Inoculation of the bladders of nonrefluxing primates with P-fimbriated *E. coli* resulted in pyelonephritis in 66% of animals. In contrast, pyelonephritis was not seen in any of the monkeys inoculated with non-P-fimbriated *E. coli*.[52]

In addition to its role in the pathogenesis of pyelonephritis through attachment to renal epithelial cells,

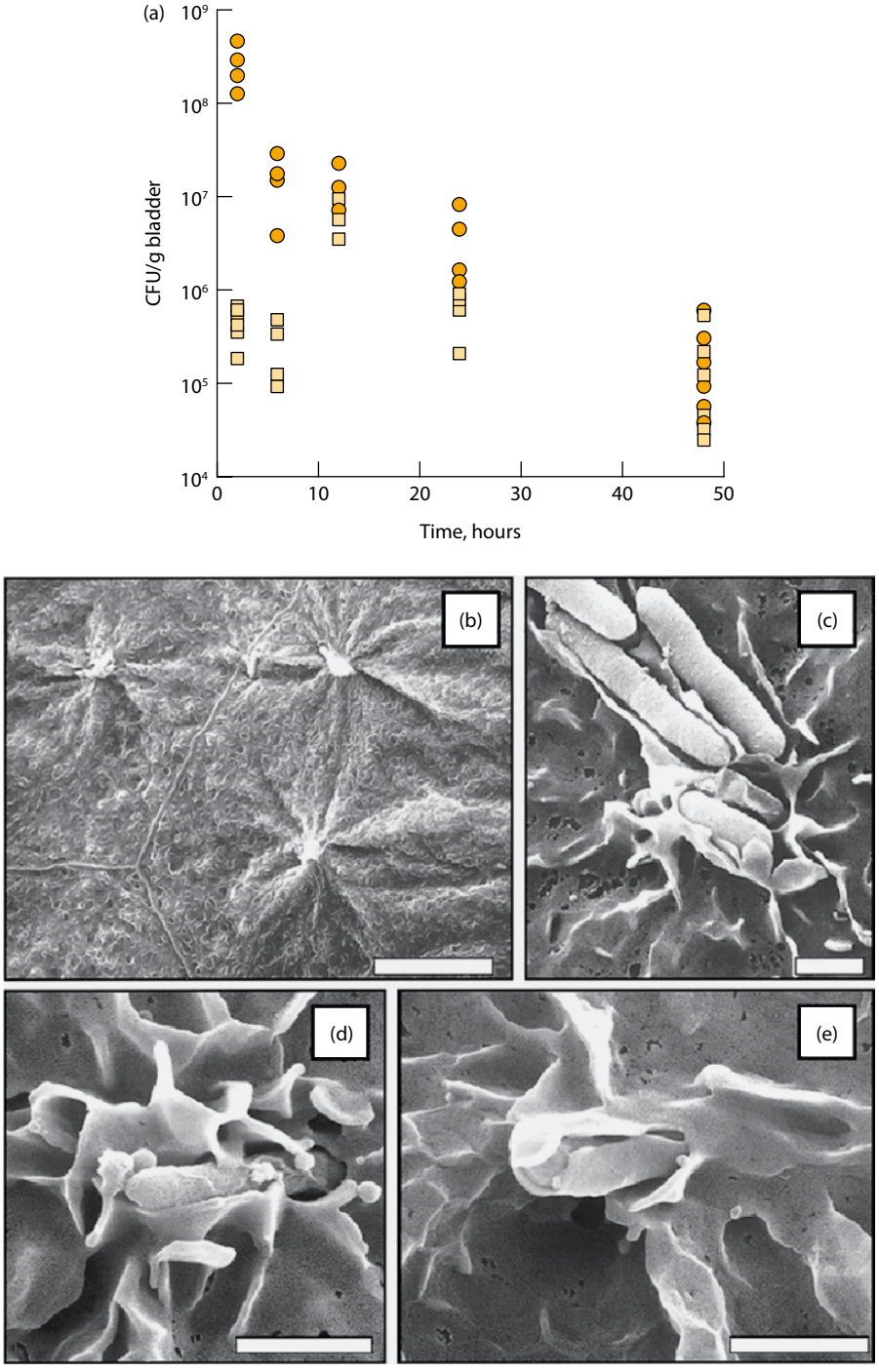

FIGURE 7.3 Kinetics of bacterial reduction in *E. coli* NU14-infected bladders and the persistence of intracellular bacteria. (a) The total numbers of bacteria per gram of mouse bladder (circles) and the numbers of gentamicin-protected bacteria (boxes) were examined per time point. (b–e) Bacteria in various stages of internalization into superficial cells at 2 h after infection with *E. coli* NU14 were detected by scanning electron microscopy (SEM). Scale bars = 10 μm (b) and 1 μm (c–e). (From Mulvey MA et al. *Science* 1998;282:1494–7.)

P-fimbriae also function to promote intestinal carriage by the host, as well as enhancing perineal colonization (see host factors) and persistence in the urinary tract. Although the data regarding intestinal carriage and perineal colonization (see host factors) by P-fimbriated *E. coli* strongly implicate the P-fimbria in the pathogenesis of infection, the data regarding bacterial persistence are less clear.

Although fimbriae appear to be the primary method by which bacteria colonize the urinary tract, there is also attachment to nonexposed ligands located in the interstitium. Dr family adhesins are surface structures that bind to bladder epithelium and type IV collagen on basement membranes. They are associated with cell invasion in vitro and contribute to pathogenesis in animal models.[53,54]

UpaG is a nonfimbrial adhesin autotransporter that promotes cell aggregation and the formation of biofilms, and mediates adhesion to human bladder epithelial cells.[55] Secondary binding to fibronectin occurs by means of fimbria encoded by pap, papG, sfa, afa, and prsG DNA sequences, a feature also more common in pyelonephritogenic strains than in strains causing cystitis or ABU.[56,57] Other adhesins may actually play a protective role by preventing UTI through competitive binding. For example, S-fimbria and type 1 fimbria bind to the Tamm–Horsfall protein and low-molecular-weight substances, respectively. Once bound, clearance of bacteria by periodic shedding of these soluble bacteria–protein complexes in the urine offers a theoretical advantage by reducing the number of infecting organisms.

Some data suggest that an organism's phenotype is variable, first facilitating colonization of the uroepithelium, and then undergoing specific changes to evade eradication by the host's immune response.[58] For example, some type 1 bacteria do reach the renal parenchyma (as in the case of VUR). These bacteria, however, must then escape type 1 fimbria-specific neutrophil receptors. In vitro studies have demonstrated that neutrophils elicit a more severe inflammatory response in the presence of type 1–fimbriated strains than when in the presence of a mutant strain lacking the type 1 fimbria.[45] Phase variation to non–type 1–fimbriated strains is known to occur, thereby conferring a potentially protective advantage. Despite this apparently unified view of bacterial virulence, several studies also exist to challenge any attempt to simplify the complex interaction between bacteria and host.[59,60] In fact, the appearance of P-fimbriated strains in the periurethral region of girls at risk for cystitis does not inevitably result in urinary infection.[61] Thus, bacterial virulence properties should not be the sole focus of blame in the development of UTI. Host risk factors probably are of equal, if not greater, significance.

Despite its significance, bacterial adherence is only one of several factors believed to have a role in infection. Other bacterial virulence factors and host defense factors may play an even greater role in tissue invasion and inflammation. In an experimental study in mice, the presence of P-fimbriae was necessary for colonization of the upper urinary tract but did not produce tissue invasion unless combined with other virulence factors.[62] Similarly, in a clinical study that employed dimercaptosuccinic acid (DMSA) renal scans to document acute inflammatory parenchymal damage in children with febrile UTI, no difference in the prevalence of P-fimbriated *E. coli* was found in children with an abnormal scan compared with those who had a normal scan.[63] Likewise, renal scarring has been reported to be more common following pyelonephritis caused by non–*E. coli* organisms when compared with those caused by P-fimbriated *E. coli*.[64,65]

Other Virulence Factors

Endotoxin: A lipolysaccharide present in the bacterium's cell wall, endotoxin is responsible for initiating the acute inflammatory response common to gram-negative infections. This same inflammatory response that eradicates the bacteria probably also leads to postpyelonephritic scarring.

Cytotoxic necrotizing factor 1 (CNF-1): CNF-1, secreted by some strains of bacteria as they invade the uropethilial cell, binds to members of the Rho family of GTP binding proteins (Rho, Rac, and Cdc42), resulting in cytoskeleton rearrangements in host cells, as well as modifications to uroepithelial cell apoptotic processes, that appear to permit bacterial invasion and permanence in the urinary tract.[66] It has been demonstrated that the antiapoptotic property of CNF-1 is dependent on the Rac-induced activation of the phosphoinositide 3-kinase (PI3K) pathway and the Bcl-2-dependent remodeling of the mitochondrial network in epithelial cells.[67] Thus, CNF-1 appears to facilitate bacterial persistence within the uroepithelial cells by opposing the natural tendency of uroepithelial cells to apoptose once infected. Therefore, CNF-1 is a fitness factor for infection, not a requirement.[68]

Hemolysin: Hemolysin is another recognized virulence property capable of damaging renal tubular cells, in vitro. Encoded by the hlyCABD operon, hemolysin stimulates cytokine production and leads to an inflammatory response that contributes to epithelial damage and bladder hemorrhage in vivo and is implicated in causing renal damage and increasing risk for septicemia.[69] Hemolytic strains of *E. coli* produce more severe experimental pyelonephritis in mice.[70]

K antigen: Capsular polysaccharides afford K antigen specificity to *E. coli*. K antigen has been shown to shield bacteria from complement lysis and phagocytosis and to enhance persistence of bacteria in the kidneys of experimental mice.[71–75] It is more commonly isolated from children with clinical pyelonephritis than from children with cystitis or healthy controls.[37,73–75]

Colicin: Another protein elaborated by pyelonephritogenic *E. coli*, colicin kills other bacteria in the vicinity of the *E. coli* producing it.[70] The *colicin V plasmid* is also thought to encode for an iron uptake system that further promotes the survival and pathogenicity of colicin-producing organisms.[76]

Metal binding capacity: Most bacteria require iron for optimal growth and metabolism and have developed mechanisms to acquire iron when there is limited supply. Mediated by such proteins as *aerobactin*, the iron binding capacity has also been shown to be associated with increased virulence in epidemiological studies.[77,78] In one study, UPECs were found to have greater than 10 characterized uptake systems and transporters for acquiring iron.[79] Additional metal binding capacity is an important virulence factor as well. Uptake of heme, enterobactin, and other sidophores also helps contribute to bacterial fitness.[80] Recently, zinc acquisition via high-affinity zinc transport systems such as ZnuACB was shown to contribute to the virulence of *E. coli*.[81]

Serum resistance: In the presence of fresh human serum, many strains of *E. coli* are killed following activation of complement. Serum resistance to such killing action is another property that has been related to virulence of gram-negative bacteria both in UTIs and gram-negative bacteria.[82]

Flagella-mediated motility: Motility is mediated by complex surface structures called flagella and is another trait associated with bacterial fitness.[83] Flagella genes are poorly expressed during chronic UPEC infection in mice,

and the synthesis of flagella appears to be tightly regulated and coincides with ascension of the bacteria.[84]

Intracellular bacterial communities (IBCs): Experimentally infected mouse bladders and voided uroepithelial cell collections from humans have been used to identify IBCs. These represent clonal invasion of bladder epithelial cells that thereby protect the bacteria from both the host immune response, including neutrophils, and antibiotics. It is hypothesized that the IBCs and quiescent intracellular reservoirs might contribute to antimicrobial resistance and recurrence of UTI.[85]

Other virulence properties enhance the bacteria's ability to evade the host immune response. For example, host protein lipocalin 2, which is expressed and released by neutrophils, binds to and sequesters enterobactin, which is a necessary iron source for UPEC.[86] However, UPEC is capable of modifying enterobactin by glycosylation into salmochelin, which is not recognized and sequestered by lipocalin 2, therefore evading the host defense.[87] Some strains of *E. coli* synthesize factors that inhibit cytokine responses, enhance tolerance to reactive oxygen and nitrogen species, and encode proteins that suppress the host inflammatory response during early stages of infection.[88–93]

Role of Bacterial Virulence in Renal Scarring

Regardless of their role in the etiology of UTI, some studies suggest that there may be a paradoxical relationship between bacterial virulence, defined by P-fimbriated binding, and renal scarring. In one study of patients with recurrent pyelonephritis, virulent clones expressing P-fimbria occurred significantly less often in patients who developed scarring (22%) than in those who did not develop renal scars (62%).[49] Although the frequency of scarring among girls with VUR was 57%, in contrast to 8% of those without reflux, this alone did not explain the selection of bacteria of low virulence in those patients with scar development. Lomberg et al. concluded that reduced host resistance was essential for the tendency of renal scarring after APN.

Other evidence supports the hypothesis that bacteria with greater virulent potential, as measured by the presence of adhesins, may elicit a more rigorous inflammatory response than less virulent clones and are thus cleared more rapidly. An alternative explanation would be that children infected with more virulent bacteria present earlier with symptoms, such as fever, resulting in more prompt diagnosis and treatment. Observations in patients with bladder dysfunction and ABU have demonstrated a low prevalence of P-fimbriated *E. coli* (less than 20%), suggesting that the presence of specific attachment structures may not be necessary for bacterial persistence in the urinary tract.[72,94,95] Moreover, coincident with an inflammatory response, P- and type 1–fimbriated *E. coli* were demonstrated to be cleared more rapidly than nonfimbriated strains from individuals with bladder abnormalities.[96]

Although these virulence factors have been considered separately, their effects appear to be additive. In contrast to those with cystitis or ABU, the majority of bacterial isolates in patients with nonreflux APN express three or four virulence properties.[49] Interestingly, the frequency of P-fimbriae and other virulence factors is significantly lower in patients who have VUR. This would appear logical since, in the presence of reflux, virulence properties, such as adherence, are not necessary for bacteria to reach the upper urinary tract. It has been suggested that efforts aimed at interfering with "virulent" bacteria, such as by vaccination, may be of less value in patients with recurrent pyelonephritis and reflux, the group in whom renal scars are more likely to develop. However, others have not demonstrated a significant difference in virulence traits among pyelonephritogenic strains in patients with and without reflux.[97]

Molecular Host Defense Factors

Interacting with bacterial virulence properties are an equally important and complex number of mechanical, hydrodynamic, antiadherence, receptor-dependent, and immunologic host factors that affect an individual's susceptibility to UTI.

Antiadherence

Epidemiological and in vitro data confirm that some blood group antigens behave as bacterial receptors in addition to their long-recognized role in determining red cell phenotypes. Of the many carbohydrate antigens, the role of ABH, Lewis antigens (Le^a, Le^b, Le^x, and Le^h), P, Kell, Duffy, MNS, and Kidd systems in host susceptibility to urinary infection is now better understood. Blood group antigens can be found on the surfaces of many epithelial cells in the body, including vaginal and uroepithelial cells, and as secreted antigens in mucus, in addition to on erythrocytes.[98,99] Presumably, bacterial colonization of epithelial surfaces is facilitated by cell surface–bound antigens, while secreted antigens mitigate colonization by virtue of competitive inhibition.

Individuals belong to one of two distinct phenotypes based on the expression of ABH and Lewis antigens on cell surfaces and in secretions (Table 7.5). The secretor phenotype is characterized by ABH antigens in saliva, Le^b and Le^y antigens on epithelial cell surfaces, and Le(a–b+) erythrocytes. Nonsecretors have mucus devoid of ABH antigens, express Le^a and Le^x antigens on epithelial cells, and have Le(a+b–) erythrocytes. Those with Le(a–b–) erythrocytes can be secretors or nonsecretors, depending on the presence of ABH antigens in secretions.

Since bacterial attachment to glycoprotein (type 1 fimbria) or glycolipid (P-fimbria) receptors is critical to colonization and tissue invasion, respectively, an individual's risk for UTI may be influenced by the composition of surface receptors available for bacterial attachment. Observations

TABLE 7.5 Distribution of antigens in secretions and on epithelial cells and erythrocytes in the secretor and nonsecretor phenotypes

	Secretor	Nonsecretor
Secretions (saliva, mucus)	ABH antigens	No ABH antigens
Epithelial cells	Le^{b+}, Le^{y+}	Le^{a+}, Le^{x+}
Erythrocytes	Le^{a-}, Le^{b+} Le^{a-}, Le^{b-}	Le^{a+}, Le^{b-} Le^{a-}, Le^{b-}

by Schaeffer and coworkers in healthy women found that the profile of antigen expression on vaginal cells and in vaginal mucus correlated with the ABO phenotype and secretor status.[100] They also noted that individuals within the same blood group phenotype expressed different amounts of ABH and Lewis antigens. Moreover, longitudinal analysis demonstrated that the level of expression of these antigens fluctuated over time.[101] However, utilizing quantitative immunohistochemical techniques, Schaeffer's group did not identify an association between a particular phenotype and a positive history of UTI when controlling for secretor status.[102] Thus, despite the appealing hypothesis that some individuals may be more susceptible to bacterial colonization by virtue of genetically determined cell surface antigens, these data do not support this notion in adult women.

In children, similar associations between blood group phenotypes and the risk of UTI have been sought. Sheinfeld et al. studied the expression pattern of blood group antigens in 72 tissue specimens from children who underwent surgery for anatomic abnormalities of the urinary tract.[103] Sixty-six percent (48/72) had a history of UTI, and the remainder served as controls. Although an increased susceptibility to UTI was noted among nonsecretors compared with secretors, the high risk of UTI was most likely a consequence of the prevalence of structural abnormalities in this study population.[103] Jantausch et al. performed a more extensive analysis of blood group antigens in seven different systems and found that only the Le(a–b–) phenotype correlated with a positive history of febrile UTIs in children, yielding a threefold relative risk.[103,104] Recently, Albarus et al. sought to confirm the association between blood group phenotypes and the susceptibility to childhood febrile UTIs. In a well-matched case-control study of children with a febrile UTI during the first year of life, no such association existed.[105] If blood group phenotypes and secretor status do not influence the risk of UTI, as some data might suggest, then perhaps the susceptibility to UTI is mediated by urinary or epithelial factors that are as yet unidentified.

Urinary Inhibitors

Although urine commonly provides the appropriate environmental conditions for successful bacterial growth, several constituents within urine have been identified that inhibit bacterial growth. Normally, the pH of urine fluctuates between 4.6 and 7.2 in accordance with physiologic needs. Since the optimal pH range for bacterial growth is between 6 and 7, increases in urine acidity can limit bacterial growth. Extremes of urine osmolarity can also inhibit bacterial growth by virtue of the limited nutrients available to support replication in dilute urine (hypo-osmolarity) or from the dehydration that ensues in concentrated urine (hyperosmolarity). Additional studies have identified short, positively charged peptides, β-defensin 1 and cathelicidin LL-137, that are antimicrobial peptides, which are protective against UTI.[105–107] Specifically, mechanistic studies in the murine model suggest that these antibacterial peptides play an important role in the bladder mucosa's ability to clear bacteria.[106,108]

The Tamm–Horsfall protein, a glycoprotein secreted by luminal cells of the ascending loop of Henle, may also be protective. This glycoprotein has been shown to contain abundant mannose residues and is identical to uromucoid. In vitro studies have shown adherence of large numbers of *E. coli* with type 1 fimbria to uroepithelial cells coated with uromucoid, in contrast to poor adherence to uroepithelial cells devoid of uromucoid.[109,110] The Tamm–Horsfall protein, when secreted into human urine, will bind to type 1 fimbriae, limiting the interaction of UPEC with host uroepithelial receptors. In fact, two studies have demonstrated such binding between type 1 and S-fimbria and the Tamm–Horsfall protein.[111,112] The Tamm–Horsfall protein has also been demonstrated to bind to neutrophils, and it is believed that this interaction can mediate recognition of bacterial invasion by neutrophils.[113] A study of UTIs in infants revealed a significantly lower mean concentration of the Tamm–Horsfall protein in those with documented *E. coli* infections compared with healthy controls.[114]

Receptors

Bacterial adherence, particularly by P-fimbria on certain strains of *E. coli*, appears to be particularly significant in the pathogenesis of upper UTIs. As discussed earlier, a special class of glycosphingolipids, possessing Gal 1–4 Gal oligosaccharide, act as receptors for p-fimbriated *E. coli*.[47,48] These receptors are antigens in the P-blood group system. It is felt that host susceptibility to bacterial adherence is conferred by the P1-blood group phenotype, since this group is overrepresented in children with recurrent pyelonephritis in contrast with normal controls.[115,116] However, this overrepresentation of the P1-blood group phenotype is seen only in patients with pyelonephritis who do not have associated VUR.[116] Despite the tenuous association between nonsecretor status and an increased susceptibility to UTI, apparently as a result of diminished secretion of antiadherence factors, a recent study has identified the presence of specific attachment structures for *E. coli* in nonsecretors. Stapleton et al. have identified glycosphingolipids on vaginal and renal epithelial cells that bind each of the three major classes of *E. coli* adhesins. Of the glycosphingolipids studies, sialosyl galactosyl globoside was determined to be the preferred binding receptor for UPEC.[117] Thus, an individual's risk for UTI may be more strongly influenced by the presence of receptors for bacterial attachment, rather than the absence of blocking antigens.

Patients who are prone to UTIs seem to have higher numbers of receptors for bacterial fimbriae.[118] CXCR1 is the receptor for IL-8 and is essential for the migration and activation of neutrophils. It has been demonstrated that the CXCR1 mRNA and protein levels are significantly lower in children who are prone to pyelonephritis.[119] Supporting evidence showed that UTI-prone children had single-nucleotide polymorphisms in their CXCR1 genes when compared with pediatric control patients, confirming a genetic influence for some at-risk children.[120]

Innate Immunity

The immunologic response to UTI has been studied at both the kidney and bladder level. Understanding the immune response to infection is particularly important

because immunization is currently being explored as a possible means of preventing recurrent UTIs. Innate immune responses are induced or mediated by pattern recognition receptors, antimicrobial peptides, and neutrophils. The antibody response to infection has also been used diagnostically to localize the level of urinary infection to the upper or lower urinary tract.[121,122]

Antibody Response

The focus of most of the clinical and experimental immunologic studies of UTI has been the immune response to pyelonephritis. During APN, a systemic antibody response occurs, with antibody production primarily against the O antigen of the infecting bacteria. A diminished response is seen toward the K antigen.[37,123,124] Counteracting bacterial adherence to host epithelial cells are protective antibodies that may be passively acquired (from mother to fetus) or actively acquired through previous exposure to infection. Conversely, in the absence of protective antibodies, some individuals are at greater risk for UTI.[125] Antibodies of the immunoglobulin M (IgM), IgG, IgA, and secretory IgA type have all been demonstrated in the serum and urine of children and experimental animals with APN.[126,127] High IgG, IgA, and secretory IgA antibody levels have also been found in the urine of girls with pyelonephritis.[127] The presence of antibodies within the renal parenchyma enhances bacterial opsonization, the process by which bacteria are coated by proteins that lead to further phagocytosis.

An antibody response to pili has also been found following pyelonephritis.[128] Secretory IgA directed against pili has been recovered from the urine of patients with APN and has been shown to prevent in vitro adherence of *E. coli* to human uroepithelial cells.[129] Mannose-specific interactions between *E. coli* and the carbohydrate moiety of secretory IgA have been reported.[130] Secretory IgA, when bound to the uroepithelium, may thus offer a receptor site for bacteria. When excreted, it may result in competitive inhibition of binding.

With regard to the immune response of the bladder to urinary infection, a systemic circulating antibody response to cystitis is not seen.[127,131] However, an elevation of secretory IgA antibody in the urine has been observed in children with UTI, suggesting local antibody production.[127,132] A more recent study reported a decreased excretion rate of secretory IgA in uninfected children with a history of symptomatic infections compared with healthy controls. However, when these girls were subsequently studied at the time of symptomatic UTI, secretory IgA excretion rates were significantly higher than in controls.[133] Other evidence supporting a role for secretory IgA as a host defense factor comes from animal studies. Attempts at local immunization of the urinary tract have shown that intravesical immunization is effective against experimentally induced ascending UTI in rats.[134] The presence of secretory IgA in the urine following local bladder or vaginal immunization has been shown to decrease adherence to uroepithelial cells in this experimental model.[135,136]

The urine of newborns has nearly undetectable levels of secretory immunoglobulin A (sIgA) that increase during the first year of life, particularly in breast-fed as compared with non-breast-fed infants. Case-control studies have identified a diminished incidence of UTI in breast-fed infants, presumably related to soluble substances that are absorbed enterically and excreted into the urine. Using high-performance liquid chromatography to purify oligosaccharides in breast milk, Coppa et al. identified small-molecular-weight, neutral oligosaccharides that significantly decreased adhesion between human uroepithelial cells and *E. coli* isolated from an infant with UTI.[137] Additionally, breast milk contains T and B lymphocytes, cytokines, growth factors, and most importantly, antibodies that may act synergistically to decrease the breast-fed infant's risk of UTI.

No differences have been noted in the levels of urinary sIgA among boys and girls, and thus impaired immunity does not explain the higher incidence of UTI in infant boys compared with girls. Instead, the predominance of UTI in infant boys likely reflects local periurethral factors (especially among uncircumcised boys).[50]

Cell-Mediated Immunity

The protective role, if any, of cell-mediated immunity in UTI is controversial.[138] A T and B lymphocytic response is seen in the kidney during experimental pyelonephritis.[139] However, others have shown a depressed cell-mediated response during the early phase of renal infection when bacterial replication is maximal.[140] Although such studies have documented cell-mediated host responsiveness to bacterial infection, they have not defined the role of this process in the pathogenesis of UTI. There is no strong clinical evidence to support abnormality of cell-mediated immunity in patients prone to UTI. Experimental UTI in mice has demonstrated no increased susceptibility to *E. coli* in athymic animals (with dysfunctional cellular immune systems) and normal controls.[141] Similarly, in patients with compromised immune systems, an increased susceptibility to UTIs has not been reported. Studies to better define the role of the immune response in UTI are obviously needed.

Further evidence supports a role for the uroepithelial cell in immunity against uropathogenic bacteria. Normally, uroepithelial cells have the capacity to produce cytokines when exposed to bacteria in vivo and in cell culture systems. While some cytokines are secreted to serve as chemoattractants for inflammatory cells, others are not secreted and may play a role in the uroepithelial cells' inherent response to invasion by pathogenic bacteria (Table 7.6).

The specific stimulus for uroepithelial cell cytokine production and release appears to be components of P- and type 1 fimbria, since urinary levels of IL-6 are significantly

TABLE 7.6 Cytokine production by uroepithelial cells in the presence of uropathogenic bacteria

Cytokine	Secreted into the urine?
IL-1-α	No
IL-1-β	No
Tumor necrosis factor	No
IL-6	Yes
IL-8	Yes

greater in the presence of adhering bacteria and adhesin-positive P-fimbria.[142–144] Further in vitro studies have determined that in response to direct contact between bacterial fimbria and receptors located on the uroepithelial cell membrane, the uroepithelial cell is able to suppress bacterial growth.[145] Moreover, utilizing human uroepithelial cells in culture, Mannhardt and coworkers have demonstrated that, in individuals with a history of recurrent UTIs, a transmembrane defect impedes signal transduction within the urothelial cell, thus rendering the cell incapable of responding to bacterial attachment. These data lend support to the concept that the most important arm of cellular immunity in the urinary tract may not be T and B cells, as classically described, but instead the inherent ability of the uroepithelium to respond to bacterial invasion. The superficial layer of umbrella cells in the bladder is covered with membrane proteins known as uroplakins.[146,147] Uroplakin 1a triggers exfoliation of the bladder epithelium when stimulated by type 1 fimbriae. This exfoliation, which removes adherent bacteria, is a result of an apoptosis-like mechanism promoted by FimH.[148]

Neutrophils are the most rapid and robust responders to UTI. IL-8 is the main neutrophil attractant in humans, and studies have demonstrated its secretion by both bladder and kidney cell lines in response to UPEC.[119,149–151] In a murine model of UTI, Lundstedt et al. showed that mice lacking the murine interleukin IL-8 receptor homologue developed APN with bacteremia and renal scarring, whereas those with the intact gene did not.[119,152,153] Failure to properly activate neutrophils in the knockout mice resulted in impaired migration of neutrophils from the subepithelial space into the collecting system, termed neutrophil entrapment.[154] Recent clinical studies found significantly reduced expression of the human IL-8 receptor CXCR1 among APN-prone children compared with age-matched control subjects without UTI, suggesting that inherited genetic variants may predispose to infection.[119]

Transmembrane Signaling

Toll-like receptors (TLRs) are part of the innate defenses enabling hosts to eliminate pathogens that would lead to disease. The TLR structure is well conserved throughout evolution, and their structure and function are tightly regulated.[155] Structural variation is relatively rare, and much work is being done to identify which variations result in disease susceptibility. Thirteen TLRs have been identified in human and mouse together, with TLR10 being active in humans but not mice, while TLR11, TLR12, and TLR13 are present in mice but not humans. Among these, TLR4 has received the most recognition for its role in activating innate immunity when in the presence of gram-negative bacteria. It has been shown that TLR4 signaling can be induced by multiple mechanisms, including a P-fimbria-dependent and lipopolysaccharide-independent pathway and a lipopolysaccharide-dependent and type 1 fimbria-dependent pathway.[143,150,156] FimH can also directly interact with TRL4; however, independent of the source of stimulation, TLR4-mediated signaling results in the activation of NFκB and expression of IL-6 and IL-8.[157,158] Other TLRs utilize alternate sources for stimulation. TLR5 will produce proinflammatory factors as a result of recognition of UPEC flagella.[159] Together, these signaling receptors help with the recruitment of neutrophils to the uroepithelium.

TLR4 knockout mice develop ABU rather than severe infection, which led Ragnarsdóttir et al. to hypothesize that reduced mucosal TLR4 function may protect against symptomatic infection.[160] After sequencing the TRL4 promoter in Swedish blood donors and children with mild or severe susceptibility to UTI, they then performed a case-control study of pediatric patients with symptomatic bacteriuria or those prone to recurrent APN. The results showed that compared with symptomatic patients and healthy controls, ABU patients had fewer genotype patterns and their promoter sequence variants decreased TLR4 expression in response to infection. They concluded that genetic variation in the TLR4 promoter may be a largely overlooked mechanism to influence TLR4 expression and UTI susceptibility.[160] Additional studies demonstrated that children with asymptomatic infections have lower expression of TLR4 mRNA and protein in neutrophils than age-matched controls.[161]

Vaccines

Much of the significance of clarifying the immune response to UTI relates to the possibility of developing an effective vaccine to prevent urinary infections. Protection against experimental ascending pyelonephritis in rats has been demonstrated using isolated capsular antigen to stimulate antibody production directed at K antigen.[134] Similarly, immunization with *E. coli* P-fimbria in both mice and primates confers protection against ascending pyelonephritis, presumably by interfering with adherence of the organism to the uroepithelium.[162,163] Immunization of rats with purified type 1 fimbria also affords substantial protection against experimental ascending pyelonephritis.[164] Thankavel et al. have identified the specific subunit region within the FimH determinant of type 1 fimbria that is responsible for attachment to uroepithelial cells. Antibodies directed specifically against this region of only 25 amino acids, and no other regions on FimH or FimA subunits of type 1 fimbria, reduced experimental pyelonephritis in mice.[165] Some evidence suggests a potential role for immunization with hemolysins as well.[62] Historically, vaccines have been directed at known virulence factors, such as those listed above. More recent advances have been identified via genomic, proteomic, and metabolic screens.[166] This approach identified a number of protein vaccine candidates that are pathogen specific, antigenic, surface exposed, and expressed in vivo. Outer membrane iron receptors were discovered to meet multiple screening criteria, and recent intranasal vaccinations have been created and demonstrated to be protective against UPEC in mice.[167]

Clinical investigations have demonstrated the efficacy of acquired immunity as prophylaxis against recurrent UTIs in women and children. Both vaginal and intramuscular immunization with inactivated uropathogenic bacteria have resulted in significantly increased levels of sIgA.[168] In a small trial involving only 10 girls with recurrent UTIs and an equal number of healthy controls, intramuscular immunization also resulted in significantly fewer recurrences in the girls vaccinated.[169] Although these results are promising, the full value of such vaccines to prevent

pyelonephritis will be critically assessed only by appropriately controlled, large clinical trials.

Currently, there are no licensed UPEC vaccines available in the United States. Two formulations that are available outside the United States are Uro-Vaxom, which is a daily oral capsule containing membrane proteins from 18 *E. coli* strains, and SolcoUrovac, a vaginal suppository containing 10 heat-killed uropathogenic strains.[170,171]

Anatomical Host Defense Factors

By necessity, these host defense factors are closely interrelated to the pathogenesis of UTIs and are functional at specific sites in the urinary tract, beginning with the route of entry of bacteria.

Perineum

Considerable clinical and experimental evidence has clearly established an ascending or retrograde urethral route of entry of bacteria in the majority of UTIs. The same bacterial strains causing urinary infections can be found on perineal cultures prior to bladder invasion. This is in contrast to negative perineal cultures in healthy controls.[172–175] The usual organisms originate from fecal floras that colonize the perineum.[176] In contrast, hematogenous seeding of the urinary tract is an uncommon source of urinary infection in children. When this is the cause of a renal infection, a cortical abscess, rather than classic pyelonephritis, is more likely to occur.

An infant's initial exposure to uropathogenic bacteria occurs at the time of birth, subjecting infants born to bacilluric mothers to a fourfold greater risk of UTIs.[177,178] It has been postulated that other host defense factors mature during the first year of life, resulting in a decreased risk of both periurethral colonization and recurrent UTI. Overall, the quantities and species of colonizing bacteria in the periurethral area diminish during the first year of life until few remain at age 5 years.[172] Meanwhile, normal periurethral flora may even be protective against urinary infection by competitive interference with attachment of uropathogenic bacteria.[179,180] This potential protective effect can be altered by the administration of antimicrobial agents, given for any reason. In a study of children with first-time APN, significantly more children had been recently treated with antibiotics, usually for non-UTIs, than controls.[26] In general, the genitalia of infant boys are more heavily colonized than those of infant girls, and when colonized, infant boys carry *E. coli* more frequently than do girls. These data concur with Winberg's epidemiological findings that UTI occurs less frequently with advancing age, and that boys younger than 6 months are at greater risk than their female counterparts.[181]

Ultimately, an infant's own intestinal tract may become colonized by bacteria with uropathogenic potential. Wold et al. reported on 13 girls with ABU who underwent characterization of fecal flora. Resident strains isolated from affected girls who more commonly expressed P-fimbria were adherent to colonic epithelium in a mannose-resistant fashion, and were one of several uropathogenic serotypes present when compared with transient strains of *E. coli*.[182] Plos et al. confirmed these findings in a prospective review of fecal isolates from children with UTIs. Affected children demonstrated intestinal colonization with P-fimbriated *E. coli* more frequently than healthy controls both during infection (86% vs. 29%) and during infection-free intervals (40% vs. 29%).[183]

Since Bollgren and Winberg's original work in 1976 in school-aged girls with a history of recurrent UTIs, three additional studies have reported on the natural history of periurethral colonization.[61,172,184,185] Despite the widely accepted concept of an ascending route of infection, the mere presence of uropathogenic bacteria on the perineum did not portend symptomatic UTI. Schlager et al. studied the association between periurethral colonization and recurrent UTI in a cohort of seven toilet-trained girls (3–6 years of age).[61] Each girl underwent weekly periurethral and urinary cultures during a 6-month period immediately following her first UTI. Almost half (43%, 53/122) of the periurethral cultures were positive; however, a positive perineal culture was obtained equally as often in the absence of urinary infection as it was prior to a symptomatic recurrence. Moreover, in only one of the four recurrences was the causative organism isolated from a perineal culture. Similarly, although heavy periurethral colonization has been reported in 75%–80% of healthy infants and toddlers of both sexes, only 1%–3% become infected.[17] In a study similar to Schlager's, Brumfitt et al. found that perineal colonization by the responsible organism did not precede the symptomatic recurrent UTI in up to 34% of the adult women studied.[185] These data may reflect the transient nature of bacterial species colonizing the perineum. Alternatively, these findings may reflect the short time course between initiation of perineal colonization and symptomatic UTI by uropathogenic bacteria in certain individuals.

Although it is not unreasonable to suspect that an abrupt change in the expression of certain key virulence factors might precipitate ascent from the perineum to the bladder, some data exist to refute this hypothesis. Schlager et al. characterized the expression of six virulence factors among *E. coli* colonizing the bladder in the absence of symptoms and those causing symptomatic UTI in seven girls. Although P-fimbriae were commonly identified in infecting species of *E. coli*, none of the six virulence factors, including P-fimbria, accurately predicted which colonizing species would ultimately cause symptomatic infection.[61] Thus, although sufficient evidence exists to support bacterial ascent into the bladder from the perineum as the mode of entry, the facilitating events in that mechanism remain poorly understood.

Prepuce

Historically, a hematogenous route of infection, rather than ascent into the urinary tract from the perineum, has been suggested in the newborn. This proposal was based on the more frequent finding of bacteremia associated with UTI in this age group.[186] However, others have not substantiated a higher incidence of bacteremia in neonates compared with other infants and children with febrile UTIs.[18,63] Furthermore, the increased risk for UTI (including pyelonephritis) in uncircumcised boys compared with both girls and circumcised boys provides additional convincing

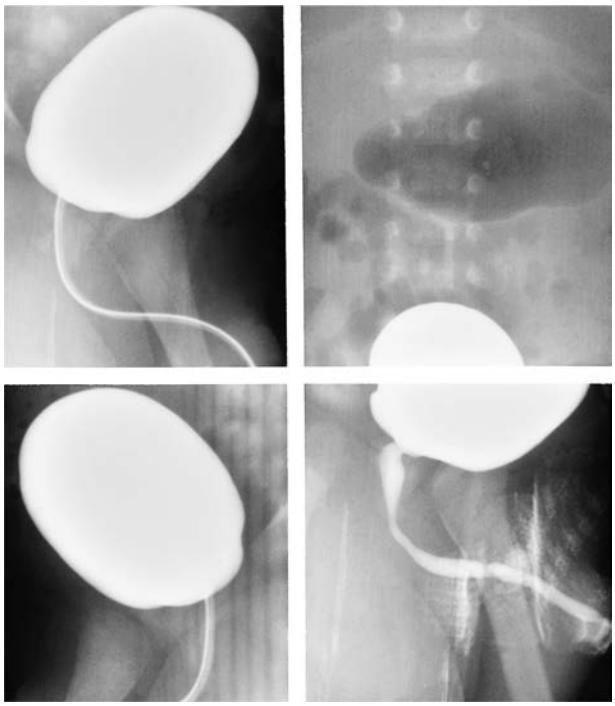

FIGURE 7.4 Voiding cystourethrogram demonstrating the absence of vesicoureteral reflux and obstructive pathology (posterior urethral valves, ureterocele) in an uncircumcised infant boy with acute pyelonephritis confirmed by ^{99m}Tc DMSA renal scan.

support for an ascending route of infection even during the first several months of life (Figure 7.4). In fact, more than 90% of boys with febrile UTIs during the first year of life are uncircumcised.[6,187] In 1985, Wiswell et al. initially found a 20-fold higher rate of UTI among infant boys who were not circumcised than among those who were (4.12% vs. 0.21%). Subsequently, two larger cohort studies by the same investigator, encompassing 637,097 infants, found the rate of UTI among uncircumcised boys to be less than that originally described, but still significantly greater (10-fold) than the incidence of UTI among those circumcised (Table 7.7).[188,189]

Evidence exists to implicate the prepuce as a reservoir for uropathogenic bacteria. Wijesina et al.[190] prospectively cultured the periurethral flora before and after circumcision in 25 boys. Prior to circumcision, 52% (13/25) of the boys were colonized by potentially uropathogenic organisms, as opposed to none of the boys after circumcision. Other studies have demonstrated that uropathogenic P-fimbriated *E. coli* adhere well to the mucosal surface of the prepuce, whereas nonpathogenic *E. coli* do not.[39,187,189]

TABLE 7.7 Incidence of UTI in female and circumcised and uncircumcised male infants (0–1 years old) born in U.S. army hospitals (1974–1983)

	Total no.	No. with UTI	Rate per 1000
All males	217,116	661	3.0
Circumcised	175,317	193	1.1
Uncircumcised	41,799	468	11.2
Females	205,212	1164	5.7

Source: Wiswell TE, Roscelli JD. *Pediatrics*, 78, 96, 1986. Reproduced with permission.

One must wonder what differs in neonatal boys, recognizing that the incidence of pyelonephritis declines throughout childhood despite the persistence of foreskin and periurethral colonization. In a retrospective study, Kim suggested that the increased risk of UTI in neonates might be related to the inability to retract the foreskin.[191] However, many boys cannot retract their prepuces until adolescence. Despite this conflicting evidence, the periurethral area of the uncircumcised infant is a closed space harboring bacteria with the potential to cause serious urinary infection in some boys.[39,192] Consequently, circumcision may help to prevent UTI in male infants by removal of the mucosal surface necessary for bacterial adherence to occur. However, since even in uncircumcised boys the incidence of UTI is low, the debate regarding routine circumcision as a preventive health measure will likely continue. Justification for circumcision in boys who have other risk factors for UTI, such as antenatal detected hydronephrosis associated with posterior urethral valves, megaureters, or high-grade VUR, is more easily argued.

Urethra

The short urethra in girls appears to be the most obvious explanation for the increased relative incidence of UTIs in girls compared with in boys after the first 6–12 months of life. Narrowed urethral caliber, historically blamed as the preeminent factor influencing susceptibility to lower UTIs in girls, does not play a role. It has long been established that the intrinsic urethral luminal size is not significantly narrower in those girls who are bacteriuric compared with those who never have been infected.[193,194] In fact, both of these studies demonstrated that the urethral diameter was slightly larger in infected groups than in those never infected. Consequently, there is no role for urethral dilatation or other cystoscopic procedures in the routine management of childhood UTIs.

Other commonly held misconceptions related to the etiology of UTIs are that improper wiping techniques and bubble baths predispose to urinary infections. However, there is no reported evidence to support these myths. The strongest evidence against improper wiping techniques being a cause of UTIs is that more than 95% of non-toilet-trained infants never develop urinary infection despite daily exposure to soiled diapers. Although bubble baths may occasionally cause dysuria from local meatal or vaginal irritation, there is no association with bacterial cystitis. More important for urethral ascent into the bladder is the ability of uropathogenic bacteria to attach to uroepithelial cells. Similar to the findings with periurethral cells, increased adherence of bacteria to uroepithelial cells has been demonstrated in children prone to urinary infections.[95,195,196] This implies a difference in host receptor density or affinity that influences an individual's susceptibility to infection.

Bladder

Vesicoureteral Reflux

Numerous reports have documented that VUR is present in 25%–50% (average 35%) of children with culture-documented UTIs.[197] In contrast, in a survey of the literature, Bailey reported an incidence of VUR in children without UTI of only 0.4%–1.8%.[198] Similar findings were reported by Ransley, who compiled voiding cystograms in 535 children without a history of UTI and found VUR in only 7 children (1.3%).[199] VUR, when present, continues to be the most significant host risk factor in the etiology of childhood pyelonephritis. The risk for both APN and subsequent renal scarring is directly related to the severity of VUR. In one prospective study of children with febrile UTIs, approximately 80% of patients with VUR demonstrated changes consistent with APN on technetium-99m (Tc-99m) DMSA renal scans, including 100% of patients with moderate to severe reflux (grades III–V/V).[63] In contrast, only 60% of patients without demonstrable reflux had evidence of APN on the DMSA scan. Kidneys associated with moderate or severe reflux were twice as likely to demonstrate abnormalities on DMSA scans (67%) when compared with kidneys with mild (32%) or no (34%) reflux. In a compilation of 10 published clinical studies of children with febrile UTIs, DMSA renal scan abnormalities have been reported in 50%–80% of children.[200] When VUR was present, approximately 80%–90% of patients had abnormal studies, including almost all with moderate or severe VUR.

The presence of VUR appears to compensate for decreased virulence of *E. coli* in patients with recurrent pyelonephritis.[49] When there is reflux of infected urine from the bladder into the upper urinary tract, bacteria do not require special virulence properties, such as cellular attaching ability, to ascend from the bladder to the kidney. In one study of girls with recurrent pyelonephritis, infections were caused by P-fimbriated *E. coli* in only 36% of those with VUR compared with 71% of those without VUR.[64] Despite the important role that VUR plays when it is present, studies of children with febrile UTIs have reported that the majority of patients (60%–68%) with abnormal DMSA renal scans demonstrating acute pyelonephritic changes do not have demonstrable VUR at the time of investigation (Figure 7.5).[200]

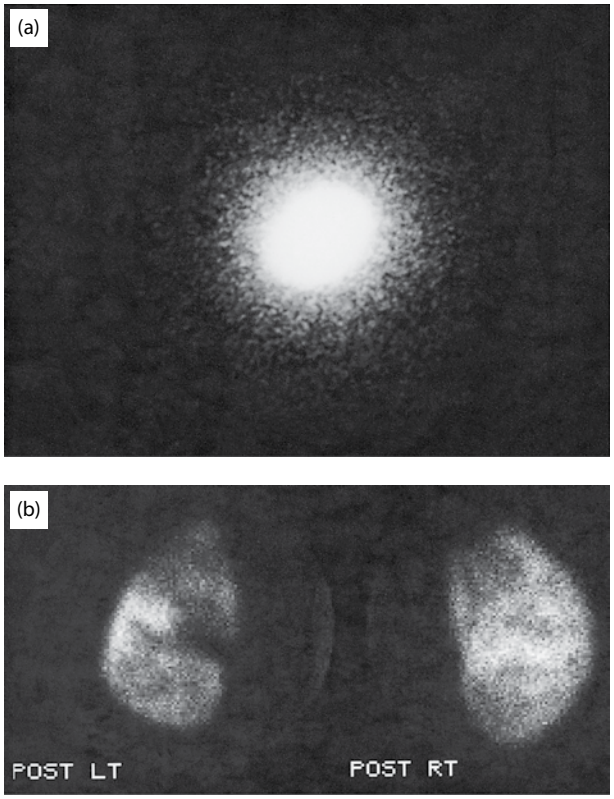

FIGURE 7.5 (a) Isocystogram demonstrating the absence of vesicoureteral reflux in a child with (b) ^{99m}Tc DMSA renal scan documented acute pyelonephritis (upper and lower poles are affected).

Dysfunctional Elimination

Abnormal voiding dynamics or bowel or bladder dysfunction is an important host risk factor for recurrent UTI, persistent VUR, failed interventional therapy, and acquired renal scarring.[201] Common voiding disorders in children prone to UTI range from the small-capacity, unstable bladder characterized by frequency, urgency, posturing, and wetting, to the infrequent voider ("lazy bladder syndrome") characterized by very infrequent voiding, a large-capacity bladder, paradoxical incontinence (wet despite a large bladder capacity), and constipation. The prevalence of some of these is listed in Table 7.7. Numerous reports have linked dysfunctional voiding and recurrent UTIs in children.[202–208] Attention has also been focused on the association between dysfunctional voiding and the presence of VUR in infants and children with recurrent UTIs.[206,209] The predisposition to recurrent UTIs and VUR in children with dysfunctional voiding is related to the presence of residual volume resulting from inadequate emptying of the bladder, increased intravesical pressure created by uninhibited bladder contractions, and bladder overdistension from infrequent voiding habits.[210] The elimination of bacteria from the bladder by frequent and complete emptying plays a significant role in preventing infection.[211] In a group of girls followed with ABU, the incidence of recurrent bacteriuria correlated directly with bladder emptying. Average residual volumes in those with ABU were 23.7 mL, whereas the mean residual volume in normal controls was 1.1 mL. On follow-up, recurrent bacteriuria was present in 75% of those with more than 5 mL of residual urine, compared with only 17% of those with less than 5 mL of residual urine.[15] The establishment of normal voiding habits in these children has been shown to reduce the incidence of recurrent UTIs.[212–214]

Initial evaluation should include obtaining a detailed history regarding urinary frequency, urgency, prolonged voiding intervals, daytime wetting, perineal or penile pain, holding maneuvers, and constipation or encopresis.[200] Squatting, delayed or infrequent micturition, urgency, constipation, and/or encopresis are significant symptoms that frequently can be elicited in 50%–94% of children with UTI.[205–207,215–219] Hellström et al. reported an abnormal voiding history in up to 49% of girls presenting between 3 and 5 years of age with their first UTI. Specifically, the presence of daytime urinary symptoms

strongly correlated with the risk for subsequent infection.[18] In a related study of the same children, Hansson found that a majority of girls with "covert" bacteriuria had urodynamic evidence of dysfunctional bladders when compared with controls.[203] Wan et al. evaluated the relationship between toileting habits and anatomic abnormalities that predispose to infection in 101 children with UTI (77 girls and 24 boys). Ninety percent of the children without structural abnormalities demonstrated dysfunctional elimination as a contributing factor to their urinary infections, compared with 40% of those patients found to have a structural abnormality, such as VUR.[220]

Similarly, there is a definite correlation between constipation and urinary incontinence, VUR, and recurrent UTIs in children.[221,222] Constipation is classically characterized by infrequent bowel movements that are large caliber and firm. This may be associated with perineal and/or abdominal pain from colonic distension. Paradoxically, children with constipation may be referred for encopresis (fecal soiling), a manifestation of the elimination of loose stool around feces impacted within the rectal vault. Unfortunately, physical examination of the constipated child is unreliable, and often a soft abdomen or empty rectal vault is encountered even when significant constipation is present radiographically. Likewise, the diagnosis of constipation can be difficult in children under 5 years who are unable to provide an accurate history.

A growing body of evidence suggests that constipation is an important facet of disordered elimination that, if appropriately managed, can help reduce the number of recurrent UTIs and promote resolution of VUR. Although this theoretically may be the result of mechanical factors related to compression of the bladder and bladder neck by a hard mass of stool, it is more likely due to the frequent coexistence of constipation with dysfunctional voiding and incomplete bladder emptying. In an epidemiological questionnaire surveying 1557 Danish children 7–8 years old (863 girls, 728 boys, 6 gender unknown), the overall prevalence of encopresis was 13.9% (5.6% girls, 8.3% boys) (Table 7.8).[223] Among the girl respondents, 75 had a history of UTI, and 13% of these suffered from encopresis versus only 6% of the girls without UTIs. Moreover, in a prospective study of 234 chronically constipated children, approximately one-third of the children demonstrated associated daytime incontinence (24%) and nighttime incontinence (34%), which reflects the degree to which bowel and bladder elimination disorders are interrelated.[213] The resolution of constipation resulted in disappearance of daytime and nighttime incontinence in a majority of children (89% and 63%, respectively). Most significant was the impact on the frequency of UTIs (approximately 10% of the total), which completely disappeared in children without structural abnormalities.

Chronic constipation also plays a role in the etiology of recurrent UTIs in children with primary VUR. Recently, Koff et al.[224] has demonstrated that up to 50% of the children with VUR who might otherwise be considered "normal" have significant disorders of elimination (Table 7.9). In children with dysfunctional voiding, the presence of residual urine and elevated voiding pressures during UTI is more likely to result in significant postpyelonephritic renal scarring than anticipated for the grade of VUR present. The risk of febrile UTI in children with VUR on prophylactic antibiotics is greater in those with bowel and bladder dysfunction 44% versus those without 13%.[201] Perhaps because of more frequent breakthrough infections while on antibacterial prophylaxis, these children have been found to be at increased risk for progressive renal scarring.[225]

Of the dysfunctional elimination symptoms, chronic constipation was the most prevalent in the presence of recurrent UTIs.[224] Many without a history of UTI had detrusor instability in the absence of infection. Among those with VUR, dysfunctional elimination significantly increased the risk of breakthrough UTIs, resulting in more frequent reimplantation surgery in these children. Endoscopic therapy results in a smaller success rate among children with bowel or bladder dysfunction than among those without dysfunctional elimination, while no such difference in success rate is seen following open surgery.[201] Additionally, the rate of postoperative UTI is 21% versus 5% for those with and without bowel or bladder dysfunction.

The rate of reflux resolution 24 months after diagnosis is less for children with bowel or bladder dysfunction than for those without (31% vs. 61%, respectively).[201] It was demonstrated that it took 1.5 years longer for primary VUR to resolve in children with dysfunctional elimination (constipation included) than in those without any elimination symptoms, despite a lower mean grade of reflux in those with dysfunctional elimination. One study by Herz et al. showed that children with APN have a higher incidence of dysfunctional elimination that is clinically more refractory to treatment, and that when dysfunctional elimination is treated effectively, the increased susceptibility to renal scarring is decreased.[226]

TABLE 7.8 Prevalence of symptoms characteristic of dysfunctional elimination in 7- to 8-year-old school children: results of Danish epidemiological questionnaire survey

	Girls (%)	Boys (%)
Urge symptoms	20	21
Day wetting	13	9
Night wetting	13	22
Nocturia	7	6
Encopresis	5	8
Emptying difficulties	8	7

Source: Hansen A et al. *Acta Pediatr* 1997;86:1345–9.

TABLE 7.9 Prevalence of elimination symptoms among 143 children with primary VUR

Symptom	Percent
Constipation	23
Bladder instability	19
Infrequent voiding	16

Source: Koff SA et al. *J Urol* 1998;160:1019–22.

Although treatment for bowel or bladder dysfunction has a distinct benefit for patients, there are no standardized treatment programs for dysfunctional elimination. The current standard of care includes common elements, such as timed voiding, relaxation measures, biofeedback if available, anticholinergic medications, and treatment for constipation.[227]

Upper Urinary Tract

Obstruction and Hydronephrosis

Urinary obstruction and/or hydronephrosis may occur at the ureteropelvic junction, the ureterovesical junction, or the posterior urethra in boys with valves. Patients with obstruction may present with severe infection. Ectopic ureters, with or without associated ureteroceles, also represent obstructed pathology. However, such anomalies are present in only a minority of children with UTIs. In fact, recent prospective studies of children presenting with first-time febrile UTIs have reported significant obstructive uropathy in less than 1%.[228] Perhaps this lower incidence is due in part to the increased detection of hydronephrosis on prenatal ultrasonography prior to the development of clinical infection. The increased predisposition to infection presumably results from impairment of urinary flow, with resultant stasis that compromises bladder and renal defense mechanisms. Both obstruction and high-grade reflux result in an increase in the residual volume of urine in the bladder or dilated urinary tract, permitting the multiplication of bacteria in the urine.[211] Obstruction also inhibits the mechanical washout or flushing effect associated with ureteral peristalsis and effective micturition, and may alter other local defense factors as well. All these factors result in increased susceptibility of the parenchyma to infection and damage.

DIAGNOSIS OF URINARY TRACT INFECTION

UTIs can be reliably diagnosed only by urine culture. Symptoms of dysuria, urgency, frequency, and enuresis are nonspecific and may be the result of vulvitis, urethritis, dysfunctional voiding, or nonspecific causes, such as dehydration associated with febrile illness. In 34 children with lower urinary symptoms alone, urine culture demonstrated significant bacteriuria in only 18%; 40% of those with sterile urine had upper respiratory tract infection.[229] Similarly, Heale et al. found that of 378 children with specific urinary complaints, only 14.3% had urinary infection. Thirty-three percent with flank pain, frequency, and/or dysuria and 31.5% with the recent onset of wetting had UTI, whereas only 4.2% with chronic nocturnal enuresis were infected.[230]

Urinalysis

Although routine urinalysis can be helpful in calling attention to those who might be infected, the association of inflammatory cells in the urine by itself is at best only about 70% reliable.[6,231,232] The finding of significant pyuria on routine urinalysis varies with the volume of urine centrifuged and examined, the force and duration of centrifugation, the volume in which cells are resuspended, and observer error.[233] Urine microscopy for bacteria significantly improves the reliability of urinalysis for the detection of urinary infection, particularly when one combines this with examination of urinary sediment for pyuria.[234] Jenkins et al.[235] reviewed approximately 40 publications reporting urine microscopy for bacteria and found a wide variation in methodology and diagnostic criteria. They concluded that the least reliable method was examination of unstained, uncentrifuged urine. When stained, centrifuged urine was examined, the sensitivity using the criteria of one or more organisms per oil immersion field was greater than 95% when compared with urine culture growing $\geq 10^5$ colony-forming units (CFU)/mL. The specificity was at least 95% when more than five organisms per oil immersion field were viewed. Hoberman et al. have recently compared quantitative urine cultures with an "enhanced" urinalysis for the detection of pyuria and bacteriuria in urine specimens obtained by catheterization in children presenting with fever. The data obtained demonstrated that UTI is best defined by more than 10 leukocytes/mm^3 on urinalysis combined with urine cultures yielding more than 50,000 CFU/mL.[236] In contrast, dipstick determination for the presence of leukocyte esterase and nitrite yielded sensitivities of only 52.9% and 31.4%, respectively, in detecting clinically significant bacteriuria (greater than 50,000 CFU/mL). In both this and another study of febrile infants, the findings of urinalysis were compared with the results of Tc-99m DMSA renal scans. Both studies concluded that APN in febrile infants is almost always associated with the finding of pyuria on urinalysis.[236,237]

Partly as a result of the technique and operator-dependent variability with urine microscopy, a number of enzymatic methods for the detection of bacteriuria or pyuria have been developed. The two most popular are the leukocyte esterase and nitrite reductase tests. These studies are inexpensive, rapid, and easy to perform.

Leukocyte Esterase Test

The leukocyte esterase dipstick test demonstrates the presence of pyuria by histochemical methods that specifically detect esterases in the neutrophils. When compared with chamber count methods, studies have reported sensitivity as high as 88%–95% for the detection of pyuria using a cutoff of 10 or more leukocytes/mm^2.[21,41,238] However, in a study that evaluated 110 children with fever and positive urine cultures, the leukocyte esterase test had sensitivities of only 52.9% and 66.7% in detecting ≥ 10 and ≥ 20 leukocytes/mm^3, respectively.[231] Furthermore, one would not anticipate this test to be any more sensitive than the finding of pyuria alone for the identification of children with positive urine cultures.

Nitrite Test

Bacteria convert urine nitrate to nitrite. The nitrite method employs reagent paper impregnated with sulfanilic acid and α-naphthylamine that form a red azo dye when in contact with nitrite. Thus, a positive colorimetric assay implies the

presence of bacteria in the bladder. However, a relatively long incubation period (4 hours) is required for conversion of nitrate to nitrite. For this reason, first morning urine sample in a toilet-trained child is the best specimen to test. A single test on a randomly collected urine specimen was reported to have a sensitivity of only 29.2%–44% on 790 urine specimens using dipsticks from two manufacturers. However, the specificity was 98% when the test was positive.[237,239] This test is not a reliable office screening method when used alone.[238]

Combining the leukocyte test and the nitrate test on a single dipstick has improved the accuracy to detect or exclude UTI. In a review of rapid methods to detect UTIs, Pezzlo reported a sensitivity of 78%–92% and a specificity of 60%–98% when using the combination test.[240] In the absence of positive Leukocyte esterase (LE) and nitrite, the diagnosis of UTI and ABU is unlikely.[241] However, the accuracy is affected by the probability of the patient being infected based on clinical findings.[240,242] Accordingly, urine culture may be omitted when the dipstick test is negative only when there is limited suspicion for UTI based on clinical symptoms. Conversely, urine culture should be obtained in any patient suspected of having a UTI or in whom the dipstick test is positive.

Urine Culture

In the pre-toilet-trained group, the urine specimen is often obtained by applying a collection bag. The results are reliable only when the specimen is negative. Contamination is directly related to the length of time the bag is in place. If a specimen has not been obtained within 30 minutes of application, reliability begins to decrease. Removing the appliance and plating or refrigerating the urine immediately after the child voids is paramount. Having the parent apply the bag before leaving for the physician's office in an effort to shorten the wait is acceptable only when the cultured specimen is negative. When confirmation of voided urine or immediate treatment is necessary, bladder catheterization or SPA should be employed. A feeding tube (8–10 French) inserted only a few centimeters into the bladder is ideal for catheterization. In girls and boys who can void on command, midstream specimens are more reliable than bag-collected specimens.

Young children are particularly favorable candidates for SPA because of the abdominal location of their urinary bladders. However, the procedure cannot be expected to be successful when the bladder is empty. This is the major drawback of SPA. If urine is not obtained initially, time should not be wasted in a sick child who requires antibiotic treatment. Urethral catheterization should be done. SPA is performed after first cleaning the suprapubic area with an antiseptic solution. A 21- to 25-gauge needle is inserted perpendicular to the patient in the midline one finger breadth above the symphysis. Although a local anesthetic can first be infiltrated, this appears unnecessary and may actually cause more pain than a quick in-and-out aspiration. It is practical to apply a U-bag to the perineum prior to cleansing the abdomen. Many times, the child voids during preparation for aspiration, obviating the necessity for the procedure if the voided urine is immediately plated or refrigerated.

It has often been stated that "any number of bacteria" obtained by SPA is significant. Since the bladder is a reservoir and this method of collection depicts the number of bacteria in that reservoir, one should not anticipate colony counts significantly different from those properly collected by other means. Ginsburg and McCracken found ≥100,000 CFU/mL in 96% and 40,000–80,000 in the remaining 4% of 100 febrile infants with bacteriuria demonstrated on SPA.[6] None showed fewer than 40,000 colonies. Nelson and Peters had previously reported similar results in a study of premature and term infants.[243] Hoberman et al. recently reported the results of positive urine cultures on specimens obtained by catheterization in 110 febrile infants of <2 years old.[236] Of 110 urine cultures with ≥10,000 CFU/mL, 92 (84%) had ≥100,000 CFU/mL, 10 (9%) had 50,000–99,000 CFU/mL, and only 8 (7%) had 10,000–49,000 CFU/mL. Furthermore, urine specimens with 10,000–49,000 were much more likely to yield gram-positive or mixed organisms than specimens with >50,000 CFU/mL. These authors concluded that UTI is best defined by ≥10 leukocytes/mm^3 and colony counts of ≥50,000 on catheterized specimens. Thus, colony counts from the bladder of <50,000 CFU/mL are suspect regardless of the manner in which the urine was collected.

Fevers

Traditionally, fevers of >101.5°F have been used to help define APN clinically. Studies by Biggi et al. have demonstrated that high fever is not a reliable sign to discriminate pyelonephritis documented on a DMSA scan from a lower UTI.[244] They showed that the sensitivity and specificity of a temperature greater than 39.1°C to diagnose pyelonephritis were 64% and 38%, respectively. This was supported by a small pilot study by Farnsworth et al. that demonstrated that 41% of individuals who had parenchymal involvement seen on DMSA scan were afebrile.[245]

Biomarkers

Biomarkers are defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention."[246] Effective biomarkers can be used to monitor disease burden, predict therapeutic response, and measure adverse effects. Diagnostic biomarkers may be one of the most difficult to develop because rigorous negative and/or positive predictive values are needed for the biomarker to be clinically applicable and not just statistically significant.[247] Unfortunately, variation in study designs and lack of appropriate prospective clinical studies have made it difficult to define clinically applicable markers for VUR and APN.

There have been many attempts to identify biomarkers for APN and/or renal scarring that have not proved to be clinically significant.

Angiotensin-converting enzyme genotype: Hohenfellner et al. reported that patients with the angiotensin-converting enzyme (ACE) DD genotype were at higher risk for renal parenchymal damage and glomerular filtration rate (GFR) reduction secondary to obstruction or VUR than those with

the II or DI genotype.[248] These data were disputed by others who demonstrated no difference in renal scarring regardless of VUR for any genotype.[249]

N-acetyl-β-glucosaminidase and β-2-microglobulin: Others have evaluated the role of urinary N-acetyl-β-glucosaminidase (NAG) (a renal tubular enzyme thought to be a marker of tubular damage) and β-2-microglobulin (β_2M) (a low-molecular-weight circulating protein with increased fractional excretion in children with tubulointerstitial disease) in the diagnosis of pyelonephritis in febrile children. Unfortunately, elevation of this urinary marker has been found in both children with febrile UTIs and children with sterile urine who had severe renal scarring associated with high-grade VUR, making these markers unreliable for the diagnosis of APN.[104,250,251]

Procalcitonin: Procalcitonin (PCT), on the other hand, has been studied in depth and is emerging as an effective biomarker to differentiate lower UTI from pyelonephritis in the pediatric age group. First described by Assicot et al. as a marker of bacterial invasion, PCT is produced in C cells of the thyroid gland in healthy humans with upregulation during a severe bacterial infection. It is also produced by the monocyte–macrophage system locally at the site of inflammation.[252] Gervaix et al. demonstrated a higher level of PCT in the setting of renal parenchymal damage on DMSA scans than in patients who had lower UTI.[253] Pecile et al. prospectively showed that mean PCT increased proportionally with the extent of renal involvement on DMSA scan, and that PCT levels at admission were lower in patients with completely reversible lesions versus those with partially reversible lesions or renal scarring.[254] Benador et al. confirmed these findings in a prospective study of 80 children evaluating PCT, C-reactive protein (CRP), and white blood cell (WBC) count in pyelonephritis and lower UTI. They demonstrated statistically significant differences between the two groups for all three parameters; however, only PCT had good correlation with increasing severity of scintigraphic changes noted on DMSA (PCT of 5.37 μg/L in pyelonephritis group vs. 0.38 in the lower UTI group).[255] Similarly, Gürgöze et al. conducted a prospective study of 76 children with UTI using a PCT cutoff of 0.5 μg/mL to diagnose pyelonephritis demonstrated by DMSA scan. In this study, the sensitivity and specificity for detection of acute pyelonephritic changes on DMSA scans were 94% and 58%, respectively.[256] Using the same cutoff value for PCT, a similar study found a sensitivity of 94.1% and specificity of 89.7% for the detection of APN.[257] Sheu et al. recently reported a prospective study of 112 children less than 2 years of age with their first known febrile UTI. All were evaluated with PCT, CRP, and serum WBC counts at presentation before antibiotics were started. All had a DMSA scan within 5 days of admission and again at 6 months. Using a cutoff value of 1.0 μg/mL, they reported a sensitivity of 82% and specificity of 92% for DMSA-proven APN. They also found that a cutoff value of 3.5 μg/mL had an 18 times increased risk for the development of subsequent renal scarring.[258]

In addition to pyelonephritis versus lower UTI, PCT had been investigated as a biomarker for prediction of high-grade VUR. Leroy et al. reviewed 12 studies representing 526 patients where a PCT-preferred threshold of 0.5 ng/mL was associated with VUR grade III or greater as a continuous and binary variable with a sensitivity of 83% and specificity of 43%.[259] This idea is supported in a study that determines PCT to be a good predictor of VUR in children with first febrile UTI; however, other studies dispute these claims.[255,260]

Interleukins: IL-8 had been shown to be increased during acute UTI and may help identify children with VUR.[261] Jantausch et al. conducted a prospective study on children age 0–12 years with positive urine cultures versus controlled matched febrile subjects with infections other than UTI. At the time of admission, the median urinary IL-6 concentration for subjects with proven bacterial UTI was 397 pg/mL versus 0 pg/mL for the controls. The median IL-8 concentration for the bacterial UTI group was 5809 pg/mL versus 0 pg/mL for the controls.[262] Additional studies suggest that gene polymorphisms of IL-8 may play a role in identifying children who are susceptible to pyelonephritis with or without VUR.[263] IL-6 and IL-8 have been studied to differentiate between pyelonephritis and lower UTI. Sheu et al. investigated the role of IL-6 and IL-8 in diagnosing APN.[264] APN was confirmed with DMSA scan in 78 children with first febrile UTI. The initial values of both interleukins, IL-6 and IL-8, in serum and urine were significantly higher in patients with APN than in those with lower UTI and healthy controls. IL-6 in serum and urine significantly correlated with each other and with the presence of fever, elevated CRP, and leukocytes in the urine. Serum IL-8 and urinary IL-8 significantly correlated with each other but not with clinical symptoms.[264] However, ongoing research is needed to confirm the clinical application of these results since others, such as Krzemień et al., have showed no difference in urinary IL-6 and IL-8 in subjects with APN and those with lower UTI.[265]

WBC: WBC counts of >14,601 cells/mm^3 have a sensitivity and specificity of 56% and 58% to diagnose pyelonephritis.[244]

CRP: The CRP is 64% sensitive and 68% specific for diagnosis of pyelonephritis.[247]

ESR: The sensitivity of the erythrocyte sedimentation rate (ESR) to determine renal parenchymal damage varies with the cutoff. Garin et al. performed a retrospective study using a cutoff of >10 mm/h for ESR that yielded a sensitivity and specificity of 100% and 8%, respectively.[266] However, in a prospective study using a cutoff of >68 mm/h for ESR, Biggi et al. reported a sensitivity and specificity of 48% and 50%, respectively.[244]

At the present time, additional prospective studies are needed to confirm the accuracy of candidate biomarkers for the detection of APN and/or subsequent renal scarring. If these prove to be reliable, evaluation with biomarkers at the time of presentation with UTI could be used to direct a more selective approach to imaging of children.

Proteomics

Proteomics is a rapid screening tool used for identifying new targets of interest and characterizing the protein content within cells, tissues, body fluids, and whole organisms at a particular stage or condition. Its goal is to analyze all proteins in a particular sample and determine splices and modifications to search for biological and clinical

relevance.[247] Increased understanding of the changing proteome during disease has the potential to identify many new biomarkers of disease and new therapeutic targets of disease. To date, potential biomarkers have been discovered using urine proteomics that are clinicaly applied in renal transplant, allograft nephropathy, focal segmental glomerosclerosis, renal and bladder cancer, and others.[267–275] Lee et al. have demonstrated a potential set of markers related to normal nephrogenesis and developmental maturation in rodent kidneys.[276] These studies suggest that there is significant potential for proteomics to facilitate the discovery of future biomarkers.

CLINICAL PRESENTATION AND LOCALIZATION

As one would anticipate, the classic signs and symptoms for UTI are usually lacking in the very young. Instead, nonspecific symptoms, such as irritability, poor feeding, failure to gain weight, vomiting, and diarrhea, may be the only signs suggestive of an underlying problem (Table 7.9). In one study of children with symptomatic urinary infections, only 9% of 78 infants were initially referred with a suspected diagnosis of UTI.[277] Often absent in neonates, fever is present in most infants between 1 and 12 months old who present with symptomatic UTIs.[5,17,19] In fact, UTIs have been described as one of the most common serious bacterial illnesses among febrile infants and young children, with a reported prevalence ranging from 4.1% to 7.5%.[236] In one study of 945 infants who presented to a pediatric emergency room with fever, the overall prevalence of UTI was 5.3%.[278] The prevalence was highest in Caucasian girls, 17% of whom had a positive urine culture. In contrast, the prevalence of UTI among African American girls was only 3.5% and among boys it was 2.5%. Another prospective study reported UTI in 7.5% of 442 infants (less than 8 weeks of age) presenting to the emergency room with a fever of ≥100.6°F (38.1°C), only half of whom had abnormal urinalyses suggestive of UTI (>5 WBCs per high-power field or any bacteria present).[279] Thus, a urine specimen for culture, preferably collected by catheterization, should be obtained routinely whenever a nonverbal, non-toilet-trained child presents with unexplained fever.

As the child becomes verbal and is toilet trained, urinary tract symptomatology is more easily detected. Fever continues to be relatively common in toddlers with first-time symptomatic infection. However, fever is not as frequently associated with recurrent and/or long-standing infection. In older children, urgency, frequency, enuresis, and dysuria are common presenting symptoms. Failure to become toilet trained at the proper age may occasionally herald underlying chronic lower urinary infection. Although urinary tract symptoms such as vaginal pain, urinary frequency, dysuria, and enuresis are common following childhood sexual abuse, actual urinary infection is not.[280]

There are few population-based studies of symptomatic UTIs in childhood. The classic epidemiologic study by Winberg et al. was carried out between 1960 and 1966 in Goteborg, Sweden.[17] Subsequently, the special organizational structure of that city's pediatric medical care has afforded unique opportunities to perform ongoing epidemiologic studies of UTIs in children. Jodal reported a follow-up prospective epidemiologic study conducted in Goteborg from 1970 to 1979.[5] There were 952 females and 225 males (4.2:1) below the age of 10 years of age who were treated for a first-time symptomatic urinary infection (Figure 7.6). Of the 225 boys, 59% presented during the first year of life. The number of boys diagnosed in the higher age groups was low, especially over age 5. The number of first infections in girls was also highest in the first year of life (19%). A gradual decrease in number of girls with first-time infections was associated with increasing age. In both girls and boys, febrile infections, presumed to be pyelonephritis, predominated during the first year of life. Acute cystitis was most commonly seen between 2 and 5 years of age in

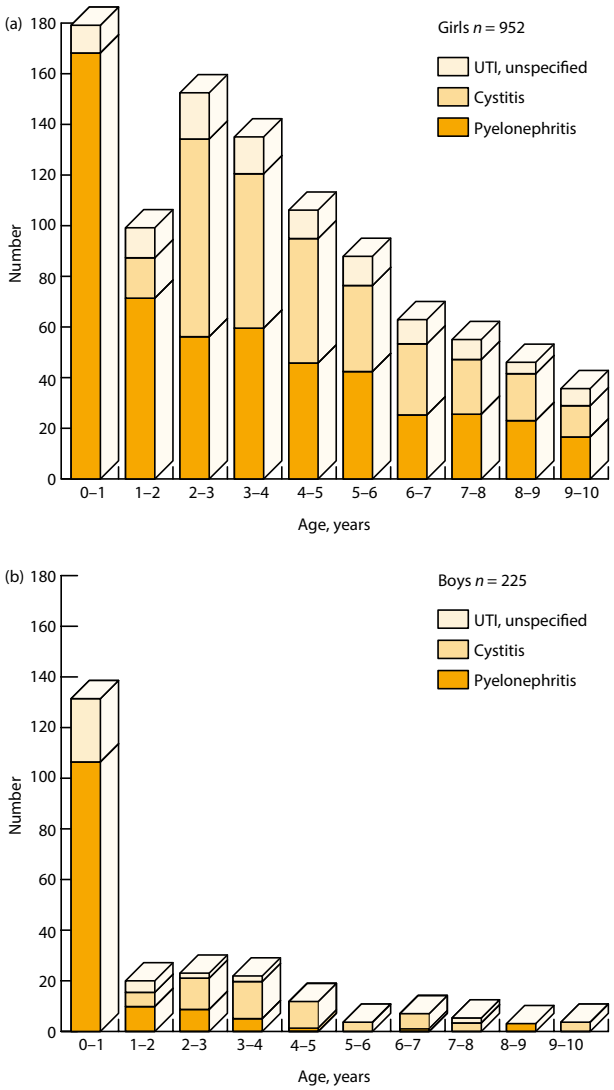

FIGURE 7.6 Children with first-time diagnosis of urinary tract infection at the Children's Hospital in Goteborg, Sweden, according to age and clinical diagnosis. (Reprinted from Jodal U. Urinary tract infection in children. In: Holliday M, Barratt TM, Avner Ed, eds. *Pediatric Nephrology*, 3rd edn. Baltimore, MD: Williams and Wilkins, 1994. With permission.)

both sexes, with a marked peak frequency in girls during the third year of life. As expected, infections during infancy were the most difficult to characterize as pyelonephritis or cystitis.

Asymptomatic Bacteriuria

The natural history and uroradiographic findings in patients with asymptomatic or covert bacteriuria vary according to the age of the patient and prior episodes of symptomatic infections. Screening bacteriuria does not necessarily represent ABU, as approximately one-third of school-aged girls with screening bacteriuria have a prior history of symptoms related to the urinary tract, and some have had previous symptomatic UTIs. It is unclear whether the prognosis is any different for children who have primary ABU compared with those in whom ABU develops following treatment of a symptomatic infection.

A study of asymptomatic and symptomatic bacteriuria in infants under 1 year of age reveals interesting differences in the two populations.[5] In 2 of 50 patients with ABU, clinical APN developed within 2 weeks of detection. The others remained free of symptoms. Mild reflux (grades I and II) was found in only five (11%). Of 45 left untreated, 36 spontaneously cleared the bacteriuria and 8 others became abacteriuric following antibiotic treatment for other reasons. Although asymptomatic recurrences developed in six (12%), no pyelonephritic recurrences occurred in this group during follow-up of at least 1 year. Follow-up urography, done in 36 patients, did not reveal any evidence of renal scarring. In contrast, among 40 infants with symptomatic infections, 1 patient had a significant ureteropelvic junction obstruction and 14 of 39 (36%) had VUR, including three with grade III or greater. Fourteen of 40 (35%) experienced recurrences, including 6 with APN and 3 with cystitis, whereas ABU was noted in 5. It was concluded that infants with ABU represent a low-risk group, with a tendency to spontaneously become abacteriuric, usually within a few months.

Considerable variation in uroradiographic findings has been reported in school-aged children found to have bacteriuria on screening. These studies have reported VUR in 19%–35% and renal scarring in 10%–26% children.[11,15,281–284] However, many of these children had a prior history of symptomatic UTIs, and others undoubtedly had infections during infancy that were overlooked or misdiagnosed. Although recurrent infections following treatment occur in up to 80%, the risk for development of APN in a girl older than 4 years of age with untreated ABU is small and seems to be associated with a change in bacterial strain, perhaps as a result of antibiotic treatment.[11,285] Follow-up by the Cardiff-Oxford Bacteriuria Study Group revealed that those school children who presented initially with a radiographically normal urinary tract remained normal in spite of persistent ABU.[286] Only in those children who had previous renal scarring did new scars or progression of scarring develop, and all these children had VUR. Other studies have shown that ABU is associated with low-virulence bacterial strains lacking the ability to adhere and cause symptoms.[51,129,287] Furthermore, there is considerable evidence that these organisms may be commensal with the host and may even protect against infection by more virulent strains.[288]

Cystitis

Acute cystitis in children is rarely associated with significant long-term morbidity. Typical symptoms that accompany acute cystitis in toilet-trained children include dysuria, frequency, urgency, and/or secondary-onset enuresis. Fever and systemic complaints are generally not a feature of the clinical picture. As previously mentioned, however, these same irritative lower tract symptoms are often seen in the absence of bacterial cystitis, mandating that a specimen for urine culture be obtained prior to institution of therapy.

Although the recurrence rate of lower UTIs is high, most cases can be considered little more than a nuisance, and recurrences tend to decrease or disappear by adolescence. However, it is worth noting that many children prone to recurrent lower UTIs have voiding dysfunction, particularly infrequent voiding. Typically, these children do not void for 1 or 2 hours after awakening in the morning, and then may void only two or three times throughout the day. Consequently, bladder capacity is abnormally large and bladder emptying is often incomplete. Often, these children also have chronic constipation, including encopresis in some. Other children with recurrent cystitis have underlying bladder instability associated with urinary frequency, urgency, and urge incontinence and posturing associated with a reduced functional bladder capacity. Girls with a history of UTI are significantly more likely to report a variety of chronic voiding disturbances than girls without a history of UTI (Table 7.10).[18,223] In some cases, recurrent UTIs may be a precipitating factor to the child's voiding disturbance. Conversely, primary bladder instability and/or infrequent voiding may itself contribute to an increased susceptibility to UTIs. In contrast to daytime voiding disorders, isolated bedwetting is rarely associated with a history of previous UTI.[18]

Approximately 10% of susceptible girls will have a recurrent infection shortly after completion of a course of antibiotic therapy. These children have chronic symptoms of bladder instability. Squatting or posturing in response to unstable bladder contractions is common in this group. Many have dysfunctional voiding associated with high voiding pressures and incomplete bladder emptying. Some also have chronic inflammatory changes of the bladder. Historically, endoscopic evaluation of these children often revealed multiple raised "cysts" in the area of the bladder

TABLE 7.10 Bacteriologically verified previous UTI in 7-year-old children

Diagnosis	Girls (%) ($n = 1719$)	Boys (%) ($n = 1834$)
Pyelonephritis	2.7	1.0
Cystitis	3.4	0.3
Unspecified UTI	1.7	0.3
Covert bacteriuria	0.6	0.1
Total	8.4	1.7

Source: Hansson S, *Scand J Urol Nephrol* 1992;141(Suppl.):47–55.

neck and trigone. Histologically, submucosal lymphoid follicles were present. Clinically, this entity has been termed cystitis cystica, although the histologic appearance suggests it would be more accurately referred to as cystitis follicularis. The presence of these follicles suggests an immunologic response to chronic infection.[289] It should be noted that treatment of these children is no longer predicated on the basis of these endoscopic findings. Rather, treatment is determined by the recurrence rate of infection and the type of underlying voiding and bowel disorder.

Pyelonephritis

Pathophysiology of Acute Pyelonephritis

APN represents the most serious type of UTI in children. It is not only responsible for greater acute morbidity, but also has the potential for causing irreversible damage. APN in older children typically presents with fever and flank pain or tenderness associated with pyuria and positive urine culture. In the majority of cases, laboratory evaluation reveals an elevated serum WBC count, ESR, and/or CRP. However, when compared directly with localization studies such as DMSA renal scans, these clinical and laboratory parameters are associated with high false-positive and/or false-negative rates.[200] This is particularly true in neonates and young infants, an age group at greatest risk for renal scarring following pyelonephritis. Neonates in particular present with nonspecific symptoms, such as irritability, poor feeding, failure to thrive, vomiting, and diarrhea. Considering that approximately half of all children with febrile UTIs present during the first year of life, the importance of early and accurate diagnosis becomes obvious (Tables 7.11 and 7.12).

Experimental studies by Roberts and others have found that bacterial adherence to uroepithelium elicits an inflammatory cascade proportional to the virulence of the infecting organism. The same acute inflammatory response that is responsible for the eradication of bacteria is also responsible for the damage to renal tissue and subsequent renal scarring.[290] Through a series of experimental studies using the primate model, Roberts has developed a unified theory of the chain of events involved in the process that ultimately leads to renal scarring (Figure 7.7). The initiating event is bacterial inoculation of the renal parenchyma that elicits both immune and inflammatory responses. Whereas either live or heat-killed bacteria can stimulate the immune response, only inoculation by live bacteria causes acute inflammation.[291] Since heat-killed bacteria do not cause renal scarring, it appears that it is the inflammation that is more important as a cause for the subsequent development of permanent renal damage. Potent cytokines induce chemotaxis of granulocytes and cellular- and humoral-mediated bacterial killing.

Studies have also reported that focal ischemia is a consequence of APN. Kaack et al. have shown that granulocyte aggregation within capillaries leads to vascular occlusion. Renal ischemia is then evidenced by a transient rise in circulating renin levels.[292] Hill and Clark found evidence of marked cortical vasoconstriction in areas of acute inflammation in rabbits with acute renal infection, with inflammatory cells obstructing the peritubular capillaries.[293] Androulakakis et al. found microvascular changes in APN in pigs using microradiological and stereomicroscopic techniques. Focal ischemia in areas involved by the acute inflammatory response was evidenced by compression of glomeruli, small peritubular capillaries, and vasa rectae, presumably from interstitial edema.[294] Using the microsphere technique, Majd and Rushton evaluated renal blood flow changes associated with APN in the refluxing piglet model. Focal renal blood flow was decreased in sites of APN identified by diminished uptake of DMSA and subsequently confirmed by histopathology. Uninvolved areas of the affected kidneys demonstrated normal blood flow comparable to that of the contralateral normal kidney.[295]

Since host-derived cytotoxins are central in the genesis of tissue suppuration, investigators have tried to understand and modify the inflammatory response. Granulocytes kill bacteria, releasing toxic enzymes (lysozymes) both within the granulocyte and into the lumen of renal tubules, which causes renal cell damage. The respiratory burst, a phenomenon universal to acute inflammatory responses, generates oxygen radicals (superoxides) that have classically been felt to mediate bacterial killing, as well as that of granulocytes and surrounding tubular cells.[296]

TABLE 7.11 Difference in micturition symptoms in girls with and without former UTI

Symptoms	Former UTI ($n = 75$) %	No History of UTI ($n = 723$) %	p Value
Day wetting	29.3	12.9	<0.0002
Bed wetting	25.3	12.4	<0.002
Prolonged voiding	33.3	17.8	<0.002
Able to void again	32.0	17.3	<0.002
Poor stream	29.3	15.8	<0.003
Manual compression of abdomen	17.3	7.3	<0.003
Staccato voiding	30.6	17.4	<0.006
Straining	17.3	8.6	<0.02
Does not reach the toilet	40.0	27.9	<0.03
Encopresis	13.3	6.0	<0.03

Source: Hansen A. et al. *Acta Pediatr* 1997;86:1345–9.

TABLE 7.12 Relationship of P-fimbria and type of UTI

	% of *E. coli* strains
Pyelonephritis	76–94
Cystitis	19–23
ABU	14–18
Fecal flora	7–16

Source: Kallenius G et al. *Lancet* 1981;II:1369; Vaisanen-Rhen V et al. *Infect Immun* 1984;43:149.

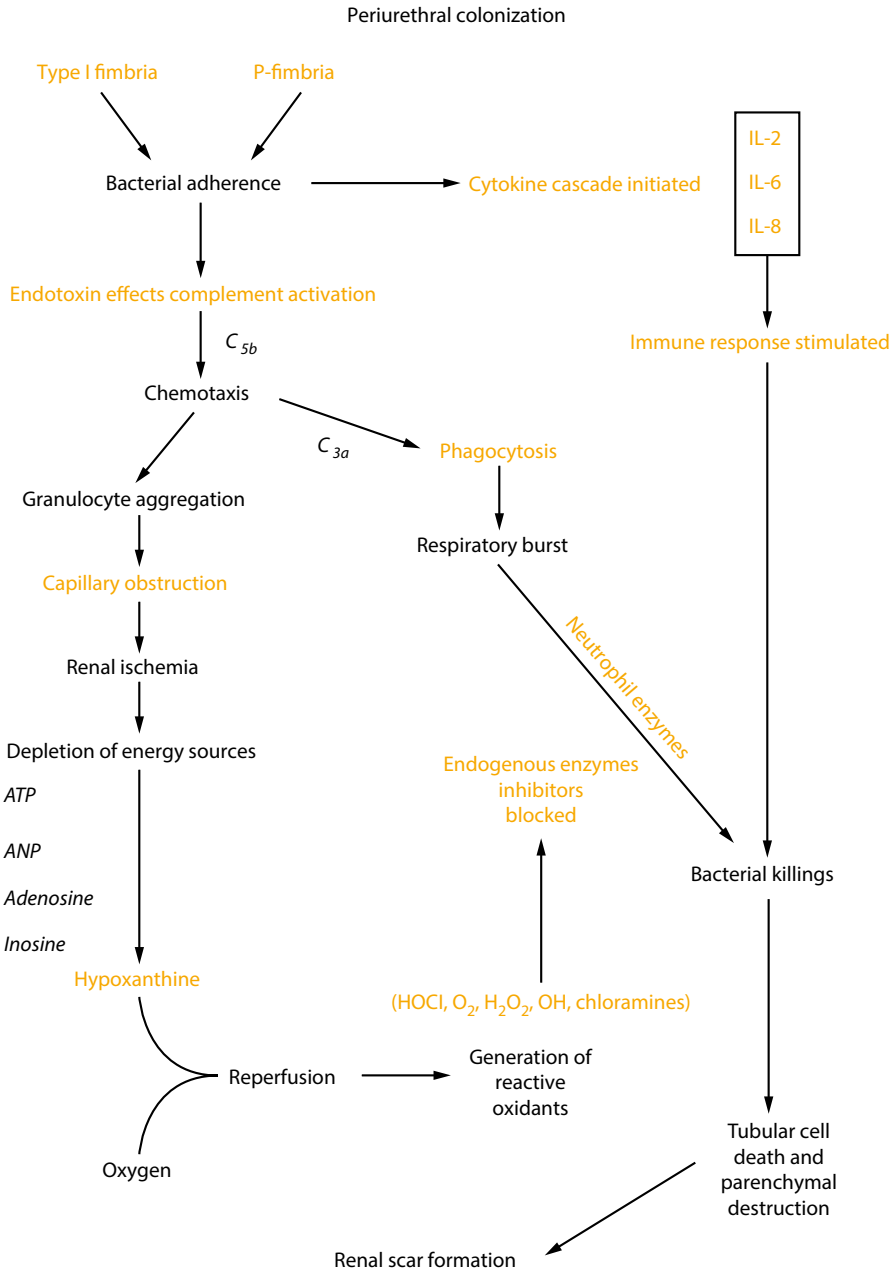

FIGURE 7.7 Diagram of the pathophysiologic events (from bacterial adherence to renal scar formation) that are characteristic of acute pyelonephritis. (From Springer Science+Business Media: *Current Topics in Pathology*, Mechanisms of renal damage in chronic pyelonephritis (reflux neuropathy), 1995, Roberts JA.)

The role of reactive oxidants, inducible nitric oxide (iNOS), and tissue-destructive proteinases in the acute inflammatory response has also been elucidated.[297] In an extensive review of the literature spanning 70 years, Weiss proposed that neutrophil-derived superoxide and oxygen radicals are merely highly reactive intermediates in the production of toxic chlorinated oxidants (e.g., hypochlorous acid and chloramines). If these chlorinated oxidants are the true mediators of tissue destruction, then inhibiting their generation should lessen tissue injury. In fact, in vitro models have demonstrated that cellular destruction could be prevented in the presence of specific inhibitors of the H_2O_2–halide–myeloperoxidase system, effectively preventing HOCl (hypochlorous acid) generation.[297] Despite this compelling evidence, Weiss's "enthusiasm" for HOCl as the sole agent in inflammation-mediated tissue destruction is tempered by the fact that living tissue perfused with HOCl solutions remains viable.[298] However, evidence suggests that the primary role for HOCl and chloramines is to neutralize circulating enzyme inhibitors that prevent the untimely digestion of host tissues by neutrophils. Thus, in the absence of significant inflammation, any enzymes released from neutrophilic lysosomes are immediately inactivated. However, once stimulated, the neutrophil can release the aforementioned oxidants into its immediate surroundings and can

create a microenvironment capable of inactivating enzyme inhibitors, activating latent neutrophil-derived enzymes, and rapidly degrading microbes, host cells, and connective substratum.[299] Tubular cell death releases the toxic inflammatory agents into the interstitium, causing further damage.

Oxygen radicals are also produced by cell reaction during reperfusion of ischemic tissue. Focal parenchymal ischemia, resulting from intravascular granulocyte aggregation and edema, occurs with bacterial infection of the renal parenchyma.[290,292,296] In ischemic tissue, hypoxanthine is produced during anaerobic metabolism of adenosine monophosphate. During reperfusion, hypoxanthine in the presence of xanthine oxidase and oxygen yields superoxides and hydrogen peroxide.[291] Treatment with allopurinol, an inhibitor of xanthine oxidase, protects against tissue damage from reperfusion injury and inflammatory damage associated with bacteria in the renal parenchyma.[291]

Thus, it appears that the interstitial damage associated with the acute inflammatory response of pyelonephritis results from ischemia-related injury and toxic enzymes. Additionally, bacterial virulence factors, such as hemolysins and lipopolysaccharides, work in concert with neutrophil-derived mediators to disrupt cellular membranes and degrade the extracellular matrix. The inflammatory process extends through the renal interstitium, thus contributing to the damage that ultimately results in irreversible renal scarring.

The impact of adjunctive corticosteroids on postinflammatory renal scarring was evaluated in the treatment of experimental pyelonephritis in the refluxing piglet model (Figure 7.8).[300] The risk of focal scarring corresponded to the severity of the initial acute pyelonephritic lesion, as determined by the percentage of renal parenchyma involved. In kidneys with mild and moderate acute pyelonephritic lesions, antibiotics alone were equally effective in preventing scarring when compared with treatment with antibiotics and steroids. However, severe pyelonephritic lesions were three times as likely to heal without scarring in animals treated with antibiotics in conjunction with steroids when compared with antibiotics alone.

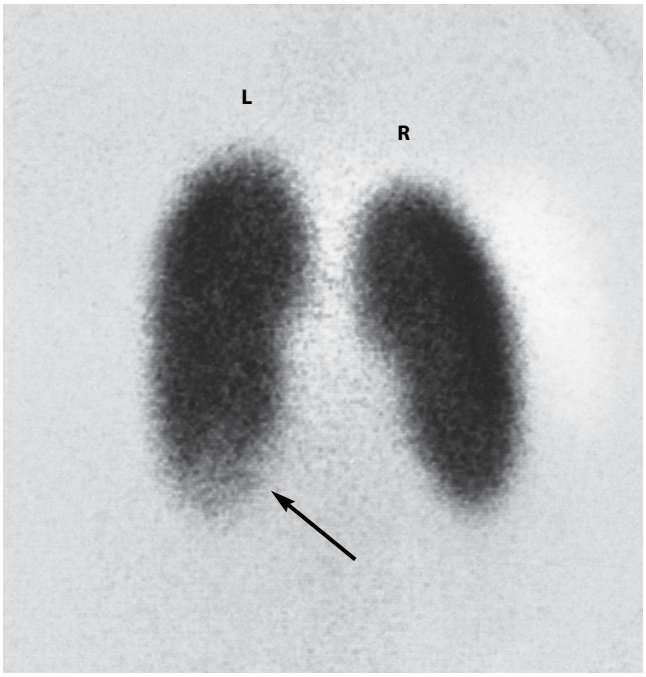

FIGURE 7.8 ^{99m}Tc DMSA renal scan obtained 1 week after introduction of infection in young pig with experimentally produced left vesicoureteral reflux. Focal decrease in uptake with preservation of renal contour is noted in left lower pole (arrow). Pathologic examination confirmed left lower pole pyelonephritis. (Reprinted from Rushton HG, Majd M. *J Urol* 1992;148(5 Pt 2):1726–32. With permission.)

Detection of Acute Pyelonephritis

Sonography and Intravenous Pyelography

Several clinical studies have clearly demonstrated that renal sonography is not reliable for the detection of APN.[301–307] In one prospective study of 91 children with culture-documented febrile UTIs, DMSA renal scans showed changes consistent with APN in 63% of the patients.[301] In contrast, sonography revealed changes consistent with APN in only 39% of the same patients. More recently, MacKenzie et al. prospectively compared the results of renal ultrasound with those from DMSA renal scans in 112 children with their first documented symptomatic UTI.[302] Although ultrasound was particularly effective in detecting dilatation of the collecting system and renal swelling, it failed to detect more than half of those patients with abnormal DMSA scans demonstrating photon-deficient areas consistent with acute inflammatory changes of pyelonephritis (Figure 7.9). This is supported by other studies demonstrating that sonography fails to identify 50% of renal abnormalities noted on DMSA (Figure 7.9).[301] Intravenous pyelography (IVP) has also been shown to be very insensitive for the detection of APN.[308]

Power Doppler

Brader et al. retrospectively studied a combination of grayscale and amplitude-coded power Doppler renal sonography in children with clinical APN and compared them with DMSA scans.[308,309] Expanding criteria for APN to include changes in flow characteristics on power Doppler, in addition to changes on grayscale sonography, they found combined sensitivities of 92.1% and a specificity of 97.8% and positive predictive value of 88%–92%. This brings into question the idea that a DMSA scan may not be necessary to confirm clinical APN. However, the availability of both pieces of equipment and a properly trained technician may be limited, and these findings need to be substantiated by other investigators.

DMSA Scintigraphy

The diagnosis of APN has traditionally been made on the basis of the classic signs and symptoms of fever and flank pain or tenderness associated with pyuria and positive urine culture. However, accurate diagnosis based solely on these parameters is often difficult, particularly in neonates and infants.[7,310] Despite the fact that the majority of patients (50%–80%) with fever and systemic clinical findings consistent with APN have abnormal DMSA scan

findings, there is still a high false-positive and/or -negative rate based on routine clinical and laboratory parameters, including fever, elevated WBC count, elevated CRP, elevated ESR, and the presence of VUR.[200]

Early clinical reports showed that renal cortical scintigraphy using Tc-99m DMSA or glucoheptonate was significantly more sensitive than intravenous urogram (IVU) and renal sonography in the detection of APN.[311–313] Subsequently, to evaluate the true sensitivity and specificity of renal cortical scintigraphy, experimental studies in an animal model were conducted using strict histopathologic criteria as the standard of reference. When DMSA was matched against histologic controls in an experimental refluxing piglet model, the sensitivity was 87%–89% and the specificity was 100% in both.[314,315] When individual pyelonephritic lesions were analyzed, DMSA scan findings correlated with histopathological changes with an overall agreement rate of 89%–94%. Those lesions not detected were microscopic foci of inflammation not evident on gross examination and not associated with significant parenchymal damage.

Not only is DMSA scintigraphy highly sensitive and specific for the diagnosis of APN, but it also provides important information regarding renal function and the extent of renal parenchymal inflammation. Documentation of renal parenchymal damage associated with APN is fundamental to understanding the roles of infection and VUR in the etiology of pyelonephritis and renal scarring.

Single-Photon Emission Computerized Tomography

The application of single-photon emission computed tomography (SPECT) to DMSA scintigraphy reportedly further enhances the sensitivity of DMSA in the detection of APN.[316–318] In clinical studies, a greater number of defects have been detected by SPECT compared with standard pinhole imaging. Obviously, in these clinical trials, histopathologic confirmation of the abnormal findings demonstrated by renal scintigraphy was not possible. To further evaluate the accuracy of SPECT imaging in the detection of APN, SPECT was compared with pinhole imaging of DMSA renal scans for the detection and localization of APN in 16 piglets (32 kidneys) with bilateral reflux of infected urine.[319] Animals were evaluated with both imaging modalities immediately prior to sacrifice at 1, 2, 3, and 10 days following the introduction of infection into their bladders. The overall sensitivity for detection of affected renal zones with histologic evidence of pyelonephritis was 86% for pinhole imaging and 91% for SPECT. The specificity was 95% for pinhole imaging and 82% for SPECT. The overall accuracy for the presence or absence of kidney involvement was 88% for both (Figure 7.10). Thus, SPECT imaging appears to be slightly more sensitive than standard pinhole imaging, but its application may result in more false-positive findings. Furthermore, it is easier to differentiate acute inflammatory changes from chronic renal scarring with pinhole imaging. Whether pinhole or SPECT imaging is utilized is to some extent dependent on the availability and experience of the imaging unit.

Other Renal Isotopes

The usefulness of an early Tc-99m mercaptoacetyltriglycine (MAG3) renal scan in predicting renal alterations

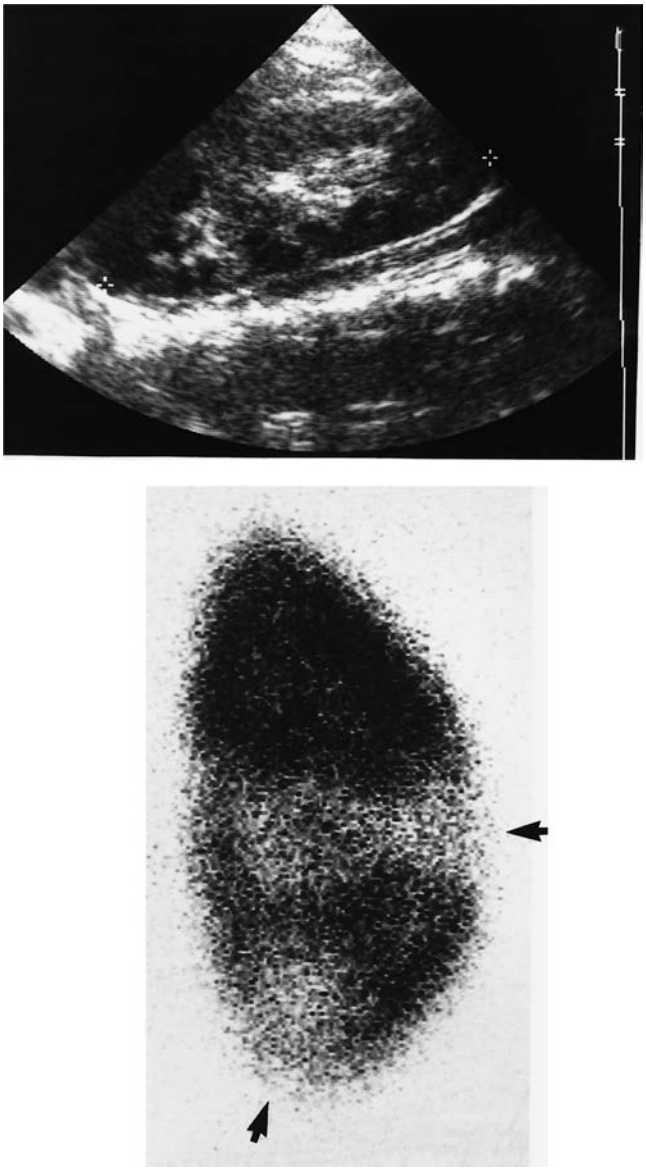

FIGURE 7.9 Normal sonogram and grossly abnormal ^{99m}Tc DMSA renal scan of right kidney showing large mid-zone and moderate lower pole photopenic lesions characteristic of acute pyelonephritis in a 4-year-old girl who presented with her first documented febrile UTI (arrows). VCUG was negative for vesicoureteral reflux.

seen on DMSA renal scans has been evaluated by Piepsz et al.[320] These investigators concluded that the accuracy of the MAG3 renal scan was population dependent. When the DMSA scan was normal or very abnormal, the MAG3 image correctly reflected the findings of the DMSA renal scan. However, when the DMSA abnormalities were less pronounced, the early MAG3 scan failed to detect about half of the cases.

Tc-99m glucoheptonate has also been used in the detection of acute inflammatory changes associated with APN.[312,313,321] Although the sensitivity and specificity of Tc-99m-labeled glucoheptonate and DMSA have not been directly compared, certain observations can be made. Approximately 60% of the administered dose of

99mTc-DMSA is tightly bound to the proximal tubular cells, and only a small amount is excreted slowly in the urine. Consequently, DMSA allows for excellent visualization of the renal parenchyma without interference from retained tracer in the collecting systems. In contrast, only about 20% of the administered dose of Tc-99m glucoheptonate is firmly bound to the tubular cells. Most of the administered dose is excreted in the urine, which allows for moderately good visualization of the renal collecting systems on the early images. This additional information makes glucoheptonate the preferred agent of some clinicians.[319] However, the quality of the delayed renal cortical images is clearly better with DMSA.

CT Scans and MRI

Computed tomography (CT) scans have become prevalent throughout most areas of medical care in the United States and have been shown to be an accurate imaging modality for the detection of acute pyelonephritic inflammatory changes in the renal parenchyma. The clarity of the images and the speed at which the test can be performed are utilized in many emergency rooms for rapid assessment and diagnosis. However, more recently the usage of CT scans has come into question within the medical community for the risk of radiation exposure to patients, as well as the increased cost to the healthcare system.

Many institutions are conducting risk–benefit analysis for CT scan radiation dose. At this time, in the United States it is estimated that only 40% of CT scanners are accredited.[322] The total dosage of radiation that puts someone at higher risk for oncologic side effects is also being debated. In the pediatric population in particular, there are concerns that some settings for dosage safety are not appropriately adjusted to weight-based criteria. Legal enforcement of regulation is beginning in some states. For instance, starting in July 2012 California state law requires radiologists to record the dose of radiation each patient receives.[320]

Consequently, CT scans are not considered to be the standard of care of pediatric patients with uncomplicated clinical pyelonephritis. It is useful for patients with equivocal ultrasound findings suspicious for renal abscesses. At many centers, magnetic resonance scans are recommended prior to CT scans in attempts to reduce radiation risk. In a clinical study for the detection of acute pyelonephritic damage in children, the sensitivity and specificity of gadolinium-enhanced MRI was equal to that of Tc-99m DMSA scanning.[323] In an experimental refluxing infected piglet model, SPECT imaging using DMSA was compared with spiral CT scanning (pre- and postcontrast), gadolinium-enhanced MRI, and power Doppler sonography in 35 infected piglets with 70 refluxing kidneys.[324] The imaging modalities were interpreted independently and compared in a blinded fashion with histopathologic findings. SPECT DMSA, spiral CT, and MRI had similar sensitivity and reliability for the detection and localization of APN, whereas power Doppler sonography was significantly less accurate (Figures 7.11 and 7.12). A distinct benefit of MRI is that it excels at tissue differentiation and can provide an estimate of renal function without ionizing radiation or iodinated contrast media.

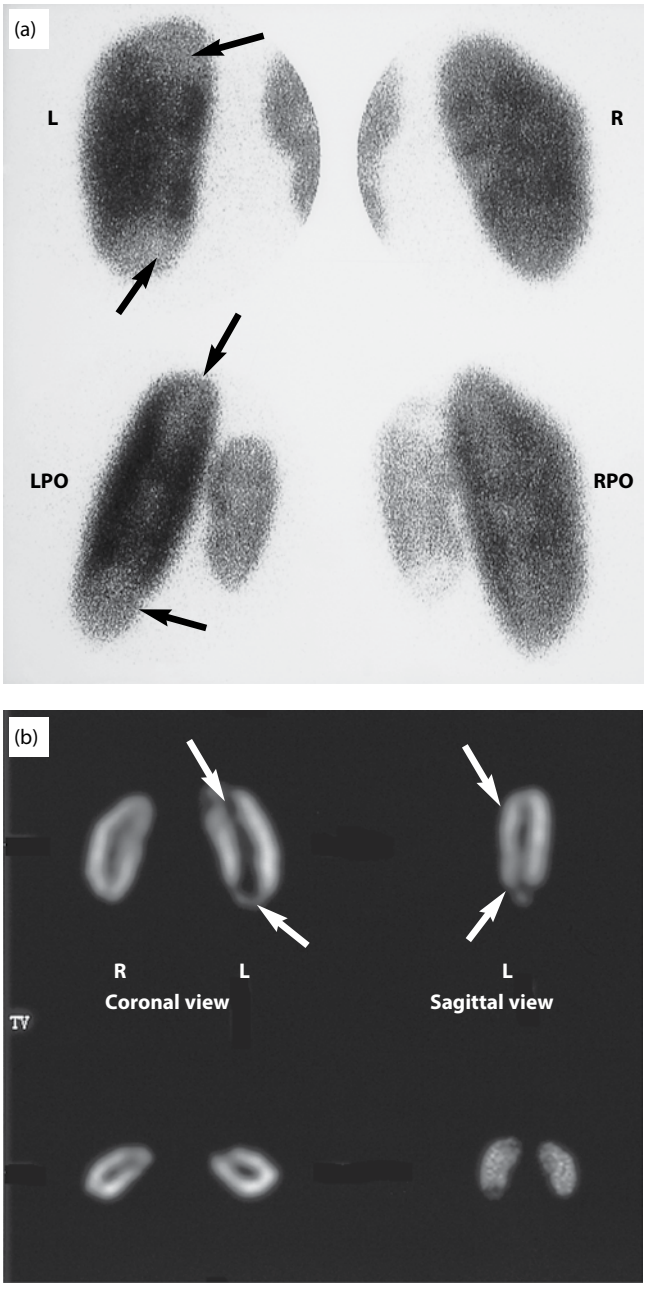

FIGURE 7.10 (a) Posterior and posterior oblique pinhole and (b) coronal and sagittal SPECT images of ^{99m}Tc DMSA renal scan in a young pig with bilateral vesicoureteral reflux and acute left pyelonephritis 48 h after introduction of *E. coli* broth into the bladder. Photopenic lesions in the left upper and lower poles are demonstrated by both modalities (arrows).

EVALUATION OF THE CHILD WITH URINARY TRACT INFECTION

Controversy continues to exist regarding when and how a child with documented UTI should be evaluated. A recent systematic overview of the literature to assess the evidence on which current recommendations for routine diagnostic imaging are based found that there were no controlled trials or analytic studies that evaluated the need for routine

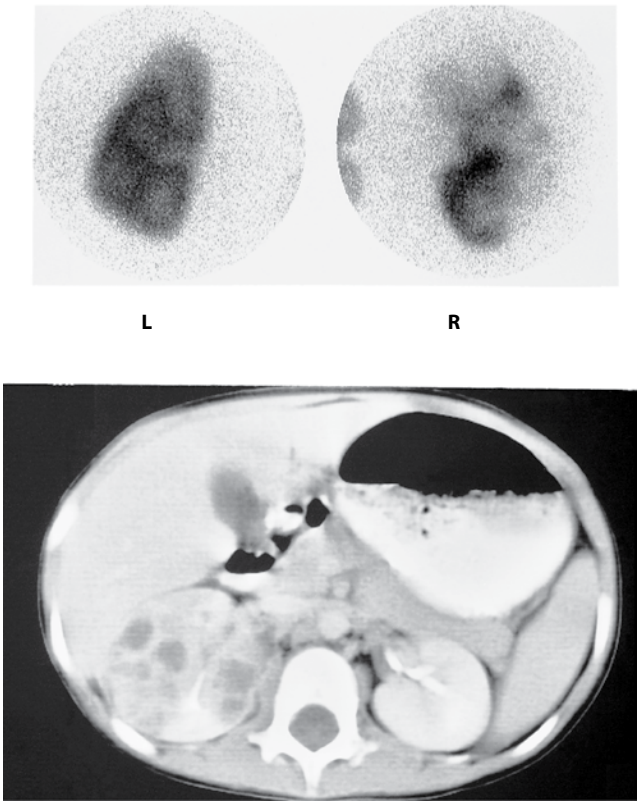

FIGURE 7.11 Severe multifocal acute pyelonephritis in the right kidney is well demonstrated on both a ^{99m}Tc DMSA renal scan and CAT scan in a 3-year-old girl with her first febrile UTI. Photopenic areas on DMSA scan correspond to attenuated hypodense lesions on CAT scan. Note diffuse right renal swelling on CAT scan.

FIGURE 7.12 Gadolinium-enhanced MRI in a young pig with bilateral vesicoureteral reflux (VUR) demonstrates multiple acute pyelonephritic lesions in both kidneys as evidenced by bright parenchymal lesions (arrows).

diagnostic imaging.[325] All reports were descriptive, and the majority were retrospective. Furthermore, none provided evidence of the impact of routine imaging on the development of renal scars and clinical outcomes in children with their first UTI.

Most pediatric urologists would agree that children under 5 years of age and boys of any age with febrile UTI or documented APN should be evaluated when infection is first recognized, to determine if further testing is needed. The key to this recommendation is adequate documentation of UTI.

The arguments in favor of early evaluation of young children following their first documented febrile UTI are based on both experimental and clinical data. Clinical and experimental studies have proved that significant renal scarring can occur after a single febrile UTI.[326,327] Furthermore, a higher incidence of renal scarring has been reported in children with VUR and recurrent UTIs than in those who have had only a single infection.[5,181,328,329] In the presence of a UTI, VUR increases the risk of pyelonephritis compared with those without VUR.[201] Recurrence of UTI within 1 year of a preceding infection occurs in approximately 30% of girls with one, 60% with two, and 75% with three prior infections.[17] Furthermore, the nonspecificity of signs and symptoms that typically accompany urinary infection in infants and toddlers often makes it impossible to determine whether an infection actually represents the first episode.[17] Additional justification for early evaluation is based on the high yield of uropathology obtained from the evaluation of children with culture-documented UTIs. Cystography in Caucasian girls with symptomatic UTIs consistently demonstrates the presence of VUR in approximately 30%–50% of cases, regardless of whether the study is requested by pediatric subspecialists (urology or nephrology) or other clinicians (pediatricians, family practitioners, or adult urologists).[5,197,330] The exception is found in African American girls with UTI, in whom the relative incidence of VUR is about one-third that of Caucasian girls.[27,63] Unfortunately, other clinical parameters have proved unreliable in distinguishing those children with UTI who also have VUR.[219] All the aforementioned factors offer a convincing argument to pursue early evaluation of young children following their first documented UTI. Waiting until a child has had two or more UTIs before proceeding with evaluation may increase the risk that permanent scarring, which might have otherwise been prevented, may occur. However, recent research demonstrated that routine cystography in every child after first febrile UTI is a nonselective, painful, irradiating, and expensive test with risk of iatrogenic UTI.[254,256,257] These randomized prospective studies have failed to demonstrate a reduction in recurrent febrile UTIs or renal scarring in patients with grades I–III VUR treated with low-dose antibiotic prophylaxis versus those followed expectantly after their first febrile UTI.[266,331] In contrast, a therapeutic benefit of antibiotic prophylaxis over a monitored surveillance program was demonstrated in the recently completed multi-institutional Swedish Reflux Trial that evaluated 203 children less than 2 years of age with grades III and IV VUR. A significant reduction of febrile UTI recurrences and new renal damage was observed in girls treated with antibiotic prophylaxis.[332]

Thus, the role of routine (invasive) cystography in all children is questioned since in the majority, who have low-grade VUR, voiding cystourethrography (VCUG) does not influence long-term outcome and management.[332,334] The counterdebate is that a subset of high-risk patients will be missed. Therefore, research is needed and ongoing to develop a more highly selective, evidence-based approach to predict which children are at high risk for febrile UTI and renal scarring.

History

Evaluation of the child with a UTI should always begin with a careful history. Because bladder emptying plays an important role in the etiology and prevention of UTI, a careful voiding history is an essential component of the workup of toilet-trained children with UTIs.[335] Many of these children also have associated constipation that may only be detected when specific questions are directed toward the patient and parents. Family history should also be obtained since heredity appears to play a role in an individual's predisposition toward infection, as evidenced by familial studies showing an increased incidence of bacteriuria in female siblings.[25] Similarly, a significant familial risk for VUR has been demonstrated when a sibling or parent has a history of having reflux.[336,337]

Physical Examination

Physical examination of the child presenting with UTI should include palpation of the abdomen for flank masses, bladder distension, and/or abdominal masses caused by fecal impaction. Although genital examination in boys should exclude significant meatal stenosis, this is an extremely rare cause of UTI. Considering the epidemiological evidence demonstrating an increased risk for UTI in uncircumcised boys, the circumcision status is of particular importance in male infants with a history of UTI. Abnormal genital findings in girls include vulvovaginitis or the presence of labial adhesions that might predispose the child to perineal colonization by bacteria. More often, labial adhesions increase the risk for contamination of "clean-catch" urine specimens for culture. In children with a significant history of voiding dysfunction associated with constipation and/or encopresis, a brief neurologic examination should include evaluation of perineal sensation, of peripheral reflexes in the lower extremities, and of the low back for sacral dimpling or cutaneous abnormalities that might suggest an underlying spinal abnormality (occult spinal dysraphism). Rectal examination for fecal impaction may be indicated in select patients if the history suggests severe constipation or encopresis, although this is rarely necessary.

Imaging

Recommended imaging studies for a child with a history of a culture-documented UTI are based, to some extent, on the experience of the radiologist and the availability of imaging modalities. Age, gender, race, and the type and frequency of UTIs must also be taken into consideration. For many years, the emphasis on the investigation of the child with UTI has centered on diagnosis of VUR. More recently, some authors have suggested that the emphasis should be focused on whether the child has renal scarring or is at risk for renal scarring.[338–343] Those favoring this "top-down" approach argue that if there is no evidence of renal damage at the time of the infection, then it is not necessary to evaluate for VUR, as the risk for future renal scarring is minimal. Consequently, these authors have recommended that the initial evaluation in children should be of the kidney, including sonography to exclude surgical conditions that predispose to infection and DMSA scintigraphy to detect acute pyelonephritic inflammation. With this approach, cystography is reserved for children with abnormal DMSA scan findings or recurrent UTIs. In contrast, most American urologists still prefer a "bottom-up" evaluation of infants and toddlers that always includes a cystogram to detect the presence of VUR, ureteroceles, posterior urethral valves in boys, or bladder wall thickening, along with a sonogram to look for obstruction, hydronephrosis, or other congenital malformations.[344,345]

Whether or not one accepts the recommendation that DMSA scintigraphy should precede VCUG in the evaluation of children with UTIs is determined in part by the goal of management of these patients. For those whose ultimate goal of treatment is the cessation of VUR, when present, VCUG will continue to be the initial study of choice. For others, whose primary goal is the detection and future prevention of pyelonephritis and new renal damage, DMSA scintigraphy may well replace VCUG as the initial investigation of children with symptomatic UTIs. MRI is currently expensive, not readily available at all institutions, and generally requires sedation for small children. Consequently, it is not used routinely for the diagnosis of febrile UTIs at this time.

Timing of Evaluation

The timing of evaluation is often a concern of the urologist, radiologist, and pediatrician. Many recommend that children requiring hospitalization should at least be screened for obstruction with an ultrasound scan prior to discharge. For those patients being evaluated with cystography, it has been suggested that this be delayed 4–6 weeks following the acute infection to avoid demonstrating transient mild reflux secondary to inflammatory changes of the ureterovesical junction. However, it is rare for reflux to be detected during infection and then disappear after treatment.[346,347] Furthermore, since the significance of reflux is greatest at the time of bacterial infection, demonstration of even transient reflux may be very meaningful. One potential disadvantage of obtaining a cystogram early in the course of a febrile infection is that ureteral dilatation secondary to the effect of endotoxins may result in overestimation of the grade of reflux.[52,348] Nevertheless, a prolonged "waiting period" is not necessary. The cystogram, when indicated, usually can be performed whenever the patient is no longer symptomatic and when the urine is sterile.[349] Regardless of when studies are performed, antibiotic prophylaxis should be considered until that time, particularly in infants or in children with a previous febrile UTI, in order to prevent reinfection.[327,349]

For patients evaluated with DMSA renal scintigraphy, the timing of the study is in part determined by the reason for the study. If one is attempting to document acute pyelonephritic inflammatory changes, the DMSA renal scan is best obtained early, within the first several days of the acute episode.[350] However, if the primary goal is to document irreversible renal scarring following an episode of infection, then the study should be delayed for 6 months following the acute infection since transient acute changes on DMSA scans can persist for up to 5 months prior to resolving.[351]

Lower Tract Imaging

Both direct and indirect cystography techniques have been used to evaluate for VUR. Direct cystography involves filling the bladder by urethral catheterization or percutaneous suprapubic infusion. Both standard contrast medium and radiolabeled nuclides are satisfactory. In boys, contrast cystography is preferred because it provides for visualization of the urethra and for grading reflux (Figure 7.13). It is also more reliable for detecting duplication, ureteral ectopia with or without ureteroceles, posterior urethral valves, bladder trabeculation, bladder diverticula, and foreign bodies. Many also prefer its use for the initial examination in girls because the grade of reflux can be determined. Historically, several methods for grading were used; however, the International Reflux Study method is most widely accepted (International Reflux Committee 1981).[352,353] A disadvantage of standard contrast cystography is the high gonadal radiation dose it entails, particularly with multiple studies or fluoroscopic monitoring. The addition of digital fluoroscopy reduces gonadal radiation exposure.[354] Using a low-dose fluoroscopic system with a computer-based video frame grabber, researchers have reported that the ovarian radiation dose compares favorably to radionuclide cystography.[355]

Direct radionuclide cystography allows continuous monitoring for reflux throughout the study without

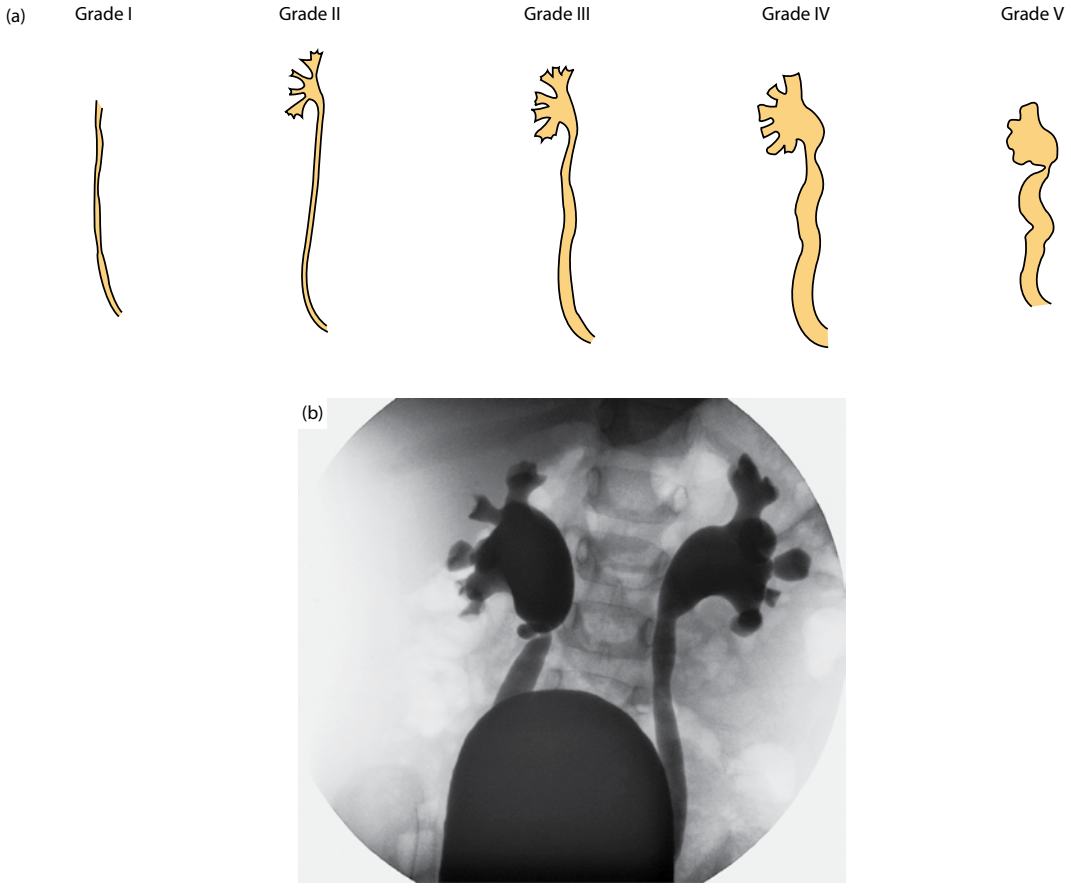

FIGURE 7.13 (a) International classification of vesicoureteral reflux: grade I, ureter only; grade II, ureter, pelvis, calices, no dilatation, normal caliceal fornices; grade III, mild or moderate dilatation and/or tortuosity of ureter, and mild or moderate dilatation of the pelvis, but no or slight blunting of the fornices; grade IV, moderate dilatation and/or tortuosity, of ureter and mild dilatation of renal pelvis and calices, complete obliteration of sharp angle of fornices but maintenance of papillary impressions in majority of calices; grade V, gross dilatation and tortuosity of ureter, gross dilatation of renal pelvis and calices, papillary impressions are no longer visible in majority of calices. (b) Voiding cystogram shows grade III VUR on the right with moderate dilatation and tortuosity of ureter, moderate dilatation of the pelvis, but slight blunting of the fornices. Grade IV reflux is seen on the left with similar dilatation of the ureter and pelvis but with obliteration of sharp angle of fornices. Papillary impressions are maintained in the majority of the calices. ([a] Modified from International Reflux Committee. Medical versus surgical treatment of primary, vesicoureteral reflux. *Pediatrics* 1981;67:392.)

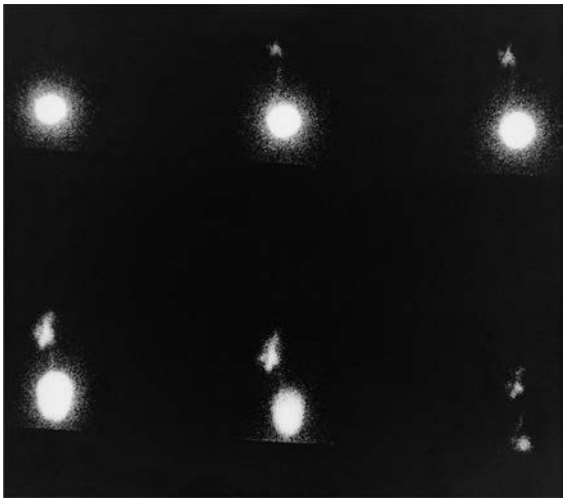

FIGURE 7.14 Isotope cystogram demonstrates mild left vesicoureteral reflux during filling (*top row*), which becomes moderate reflux when the bladder is full and during voiding (*bottom row*).

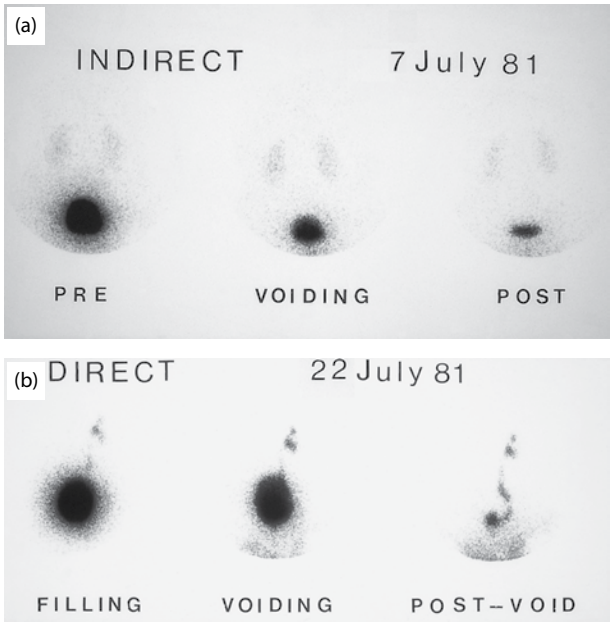

FIGURE 7.15 (a) False-negative indirect radionuclide cystogram in a 6-year-old girl. Images before and after voiding demonstrate no evidence of vesicoureteral reflux. (b) Selected images from a direct radionuclide cystogram in the same patient obtained 2 weeks after the indirect study show moderate reflux on the right during filling and voiding, and after voiding. (Reprinted from Majd M, Kass EJ, Belman AB. *Am Radiol* 1985; 28:322–8. With permission.)

additional radiation exposure. It is reported to be more sensitive than contrast cystography for the detection of reflux.[356–358] Whereas precise grading of VUR is limited, it usually can be categorized as mild, moderate, or severe (Figure 7.14). Although radionuclide cystography has been criticized for being unable to detect grade I/V VUR, one study found that direct radionuclide cystography demonstrated VUR to the renal pelvis in all 17 kidneys with grade I/V VUR on contrast cystography, again suggesting a higher sensitivity for detection of VUR.[359] The radiation dose from radionuclide cystography is reportedly less than that with standard techniques using contrast cystography, making it ideal for the follow-up of children with VUR and for following the results of antireflux surgery.[360]

Indirect radionuclide cystography uses Tc-99m diethylenetriaminepentaacetic acid (DTPA), which is excreted by glomerular filtration. The presence of reflux can be assumed when radioisotope counts increase in the renal areas after voiding. Indirect cystography is less reliable for the detection of VUR than direct radionuclide cystography, with false-negative rates ranging from 22% to 51%.[361,362] One study comparing indirect radionuclide cystography using Tc-99m MAG3 with direct cystography reported that indirect cystography was unreliable for the detection of VUR, missing approximately two-thirds of refluxing kidneys (Figure 7.15).[362] The positional instillation of contrast (PIC) cystogram is an alternative method for detecting occult VUR. It is performed under general anesthesia in the operating room with contrast instilled via cystoscope at the ureteral orifices. It has been used to detect occult VUR that standard VCUG and nuclear cystogram failed to detect. Although there are some proponents of PIC cystograms, the significance of this iatrogenically created VUR has been questioned by many, and the above-mentioned modalities for VUR identification are sensitive without the use of anesthesia.[363]

Upper Tract Imaging

Recommendations for evaluating the upper urinary tract in children presenting with UTI also vary from institution to institution. The ideal study should be painless, safe, cost-effective, and associated with minimal or no radiation, and yet should be capable of detecting clinically significant structural malformations, as well as renal scarring. Unfortunately, such an all-encompassing study does not exist.

One approach is the initial screening of all patients being evaluated for a history of UTI with a renal bladder sonogram.[364] Sonography is painless, noninvasive, simple to perform, radiation-free, and independent of renal function. It is critical that appropriate images of the ureters, bladder, and true pelvis be routinely obtained in order to detect the presence of ureteroceles or dilated ureters secondary to ureteral ectopia, ureterovesical junction obstruction, or severe VUR. To do so, the bladder should be full during the examination. A postvoiding residual can also be demonstrated at the completion of the study. In children, sonography has been found to be as sensitive as IVP for the detection of any significant renal abnormality except for uncomplicated duplication anomalies and focal renal scarring.[364–367] However, based on review of the literature, the sensitivity of renal ultrasound for predicting renal scarring has been reported to be 26.7%–41% with low positive predictive values. The sensitivity of ultrasound to predict the presence of VUR has been reported to be 65%–87%.[368] Lee et al. found that the sensitivity of ultrasound alone for predicting VUR in children less than 2 years of age was 70.1%. When renal ultrasound was combined with DMSA, the sensitivity increased to 83.6%.[369] In other retrospective studies, it has been demonstrated that only 22.8% of renal parenchymal defects demonstated by DMSA scans were detected with ultrasound.[370]

In the absence of reflux, hydronephrosis revealed by sonography is best evaluated with diuretic renography using Tc-99m DTPA or Tc-99m MAG3.[371] When combined with the findings of the renal bladder sonogram, the site of obstruction can be reliably determined in almost all cases.[104] When needed, further evaluation is best accomplished with percutaneous antegrade pyelography and pressure perfusion studies (Whitaker test).

Considering the very low incidence of surgically significant hydronephrosis presenting as UTI, some authors have questioned the role of sonography in the investigation of UTIs in children, recommending instead a cortical renal scan as the initial upper tract study of choice.[302,321,372,373] Still other authors have suggested a tailored approach to the evaluation of children with UTI, beginning with a voiding cystogram.[374,375] If no reflux is present, a renal ultrasound scan is done to exclude hydronephrosis or other upper tract malformations. Otherwise, if reflux is demonstrated, the next study would be a renal cortical scan to detect renal scarring (Figure 7.16).

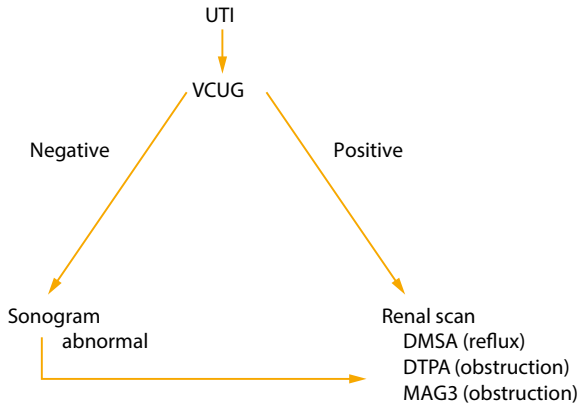

FIGURE 7.16 Algorithm for evaluation of children with urinary tract infection. (Adapted from Rushton HG. Genitourinary infections: nonspecific infections. In: Kelalis PP, King LR, Belman AB, eds. *Clinical Pediatric Urology*, 3rd edn. Philadelphia: WB Saunders, 1992. With permission.)

In clinical practice, the use of DMSA scintigraphy is best reserved for those occasions when it will influence management. DMSA scintigraphy can be helpful in the initial evaluation and follow-up of patients with VUR. For example, not all patients with VUR and breakthrough UTIs require immediate surgical intervention, particularly those with ABU (Figure 7.17).[376] In contrast, when new renal damage associated with a breakthrough UTI is objectively demonstrated by DMSA scintigraphy, antireflux surgery becomes imperative (Figure 7.18). Likewise, DMSA scintigraphy is important in the initial evaluation of infants with prenatally detected VUR, as many of these patients will have significant congenital reflux nephropathy.

DMSA scintigraphy is also particularly helpful for establishing the correct diagnosis of pyelonephritis in situations when the diagnosis is unclear based on clinical and laboratory findings, such as in neonates and young infants. Not infrequently, the diagnosis in these young children is obscured by improper urine collection techniques or the institution of antibiotics before a urine culture is obtained. Other difficult diagnostic situations include children with neuropathic bladders managed by clean intermittent catheterization.[377,378] These children are usually chronically bacteriuric; therefore, the diagnostic significance of a positive urine culture at the time of a febrile episode is lost.

Top-Down versus Bottom-Up Debate

The ideal approach to the initial radiological evaluation of children with UTI is in debate. The conventional bottom-up approach of cystography combined with sonography of the upper urinary tract, with its focus on the detection of all upper and lower tract abnormalities, is being challenged by the top-down approach, which focuses on confirming renal parenchymal involvement to identify patients who should undergo further investigation by cystography. The goal of the top-down approach is to minimize unnecessary interventions for clinically insignificant VUR and improve compliance with recommended testing.[368] Studies have

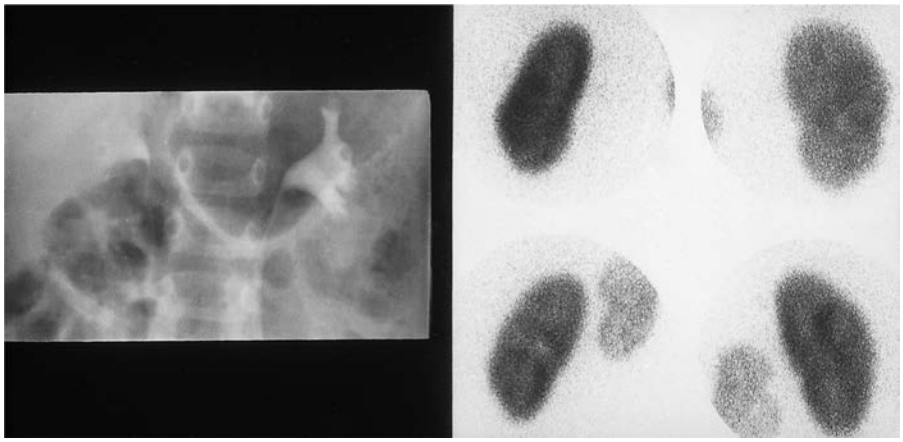

FIGURE 7.17 A 3-year-old girl with bilateral grade II vesicoureteral reflux (*left*) developed a breakthrough febrile UTI while on antibiotic prophylaxis. A ^{99m}Tc DMSA renal scan (*right*) at the time of the infections did not demonstrate any evidence of pyelonephritis or scarring. Her prophylaxis was changed and repeat isotope cystogram 1 year later revealed complete resolution of her reflux.

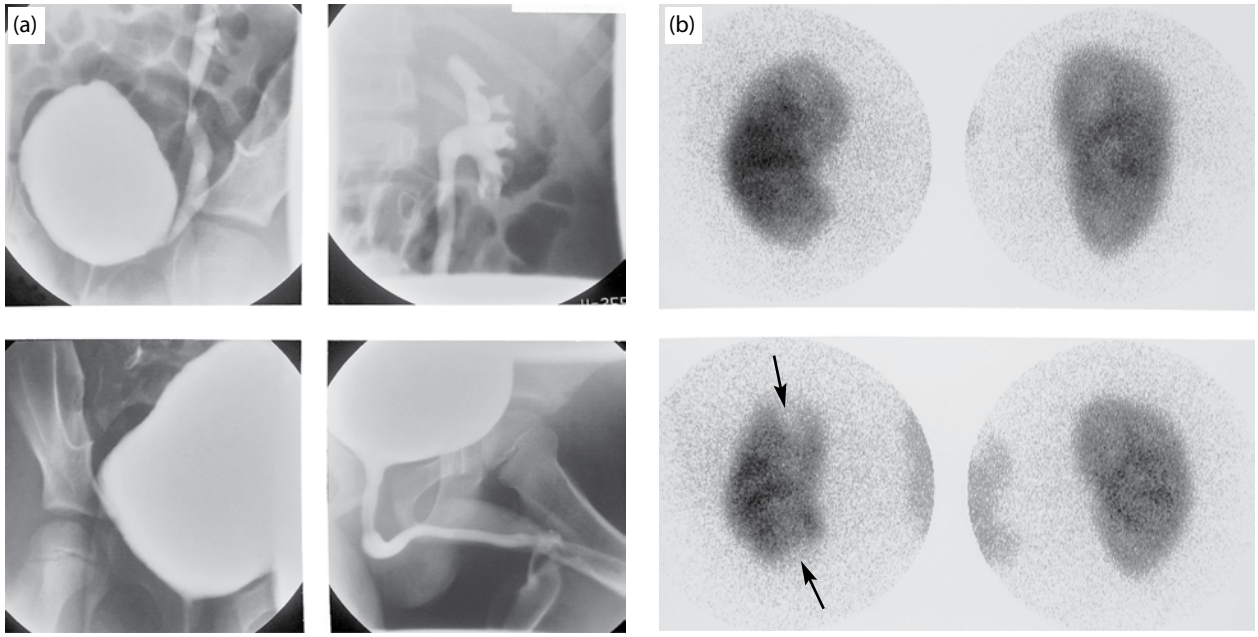

FIGURE 7.18 A 2-year-old girl presented with her first culture- documented UTI. (a) Voiding cystogram demonstrates left grade III vesicoureteral reflux. (b) (*Top*) Initial ^{99m}Tc DMSA renal scan was normal. (*Bottom*) Repeat ^{99m}Tc DMSA renal scan following a breakthrough febrile UTI reveals acute pyelonephritic changes in the left upper and lower poles (arrows). Left ureteral reimplantation was performed.

shown that compliance for follow-up imaging in infants diagnosed with febrile UTI is less than half.[379]

Traditionally, the goal of radiographic evaluation was to identify all patients with VUR; however, with the recognition that VUR is a spectrum disease, the recent shift in philosophy is to identify those subsets of patients that have clinically significant VUR based on radiological confirmation of renal involvement at the time of the UTI, as it is this group of patients who are thought to be at higher risk for renal scarring.[368] This top-down approach could potentially eliminate getting a VCUG in up to half of patients presenting with a febrile UTI and, at the same time, avoid overtreatment of those patients with clinically insignificant VUR.[380]

Mantadakis et al. performed a meta-analysis to address the controversy over what imaging needs to be performed following a first febrile UTI. They concluded that acute phase DMSA renal scintigraphy cannot be recommended as a replacement for VCUG evaluation of young children with first febrile UTI due to the fact that DMSA scans have limited ability to identify all patients with VUR.[381,382] However, several other studies suggest that children with a negative DMSA renal scan during their first febrile UTI rarely have high-grade VUR, suggesting that VCUG can be avoided in children with a negative DMSA.[380,383–386] Lee et al. pooled retrospective data from January 2001 through May 2007 in children younger than 2 years of age with first febrile UTI, comparing the sensitivity of ultrasound and DMSA scans for the diagnosis of VUR. They reported an aggregate sensitivity of DMSA scanning for identifying dilating VUR of 60% and a specificity of 65%.[369] Meanwhile, in a prospective study of 250 patients with first-time febrile UTIs who were evaluated within 2 weeks with a DMSA renal scan, Preda et al. reported a sensitivity of 96%, specificity of 55%, and negative predictive value of 99% for the detection of grades III–V VUR.[380] Herz et al. prospectively evaluated 121 children with febrile UTIs with both an acute phase DMSA at the time of infection and a repeat DMSA scan at 6 months. The acute phase DMSA scan had an odds ratio of 35.4 for the prediction of clinically significant VUR, defined as grade III or higher, or VUR associated with subsequent recurrent UTI and/or renal scarring. The acute phase DMSA scan had a sensitivity of 96%, specificity of 72%, positive predictive value of 83%, and negative predictive value of 92% for the detection of clinically significant VUR, whereas the late phase DMSA scan at 6 months had a sensitivity of only 26%.[387] Similarly, studies by Coulthard et al. and Rushton reported that more than 90% of children with grades III–V VUR demonstrated acute changes on DMSA scans.[388,389] The question becomes, what is the clinical significance of missed VUR on DMSA scan? Studies have demonstrated that patients with normal DMSA scans and higher grades of VUR who were followed had resolution or downgrading, and no new renal scarring on follow-up.[369]

One argument against using DMSA scintigraphy for the evaluation of VUR is that it is more costly than VCUG; however, it has been shown that effective use of the top-down approach in children with febrile UTI can be cost-efficient, particularly when one considers that patients evaluated with VCUG also need to undergo sonography. Furthermore, additional cost reduction with the top-down approach is achieved by avoiding unnecessary treatment and follow-up imaging of patients with clinically insignificant low-grade VUR and/or negative DMSA scans.[390] A limitation of the method, though, is that it is a more time-consuming test with technical limitations, including

the need for special equipment and skilled staff for accurate performance and interpretation.[381] In a pilot study for the Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) investigation, the methodology and image quality for DMSA scintigraphy varied between institutes despite the dissemination of methodology guidelines.[391] Seventeen percent of studies were rejected for quality issues, with the most common reason being poor image quality. Another consideration is that many younger children need to undergo sedation to avoid motion artifacts, although sedation is now also being routinely used at many pediatric hospitals for VCUGs. The overall radiation exposure is higher with DMSA scintigraphy than with fluoroscopic VCUG; however, the gonadal radiation is lower.[227,368]

Preliminary data indicate that MRI could replace DMSA scan as the renal imaging of choice after febrile UTI, as well as providing a modality for the detection of VUR, thus obviating radiation exposure.[392] Coronal fat saturated T1-weighted sequences are best for detecting renal parenchymal defects. The sensitivity of MRI for the detection of APN ranged from 77% to 100%, and the specificity ranged from 78% to 91%, when compared with DMSA scintigraphy.[393,394]

Chang et al. investigated the ability of MRI as a quantitative modality to detect renal parenchymal damage in children with VUR and UTIs.[395] Renal damage was characterized by renal scarring and grossly shrunken kidneys. The study showed a direct association between renal parenchymal loss and increasing VUR grade (nonrefluxing, low-grade VUR, and high-grade VUR). They found no significant difference between renal volumes in kidneys that demonstrated spontaneous resolution of VUR on follow-up when compared with controls. However, renal volumes for children who underwent surgical intervention were significantly decreased compared with normal controls and kidneys that exhibited spontaneous resolution.[395] At the present time, the use of MRI is limited in children by the expense of the study, the routine need for sedation, and the lack of availability of expertise or capacity in many hospitals.

In the future, the top-down approach could be even further refined by the use of biomarker profiles, such as PCT, CRP, and/or IL-8, to detect acute renal parenchymal involvement, which could then be used to select those patients who should then undergo further evaluation with appropriate imaging.

Radiation Exposure

Radiation exposure from imaging techniques is a rapidly expanding area of research. The ideal diagnostic exams would have high sensitivity, high specificity, and low radiation exposure, and be minimally invasive. The risk of cancer from radiation is actively being investigated in the adult CT literature.[396] The cost–benefit ratio of MRI versus CT scan radiation exposure is an ongoing debate in the adult literature. The radiation exposure from fluoroscopy has also been the subject of investigation.[397] With new advancements in fluoroscopy, the radiation exposure with variable-rate pulsatile fluoroscopy is reportedly 10 times less than that of the traditional continuous fluoroscopic units and 5 times less than that of a DMSA scan.[398] It must also be taken into consideration that although the DMSA scan has more radiation exposure than variable-rate fluoroscopy, the kidneys are the primary area of exposure in the DMSA scan and are known to be relatively radioresistant. In contrast, the primary area of exposure from a VCUG includes the gonads.

Renal Scarring

Partly because most renal scars that are detected in children with prior UTIs have become established by the time of initial evaluation, the pathogenesis of renal scarring remains controversial.[281,282,328] Furthermore, it has become increasingly clear that the term *renal scarring* has been applied to the end result of more than one type of pathophysiological process, including both abnormalities that are congenital and those that are acquired postnatally. The correlation between the severity of VUR and renal scarring is also well established.[5,399–401] Although the vast majority of cases of renal scarring associated with VUR are detected during the evaluation of children with UTI, studies of prenatally detected hydronephrosis secondary to high-grade VUR also have confirmed cases of congenital functional abnormalities documented by DMSA renal scintigraphy, even in the absence of infection (Figure 7.19).[402–407] Furthermore, a higher prevalence of renal scarring has been reported in children with secondary VUR associated with functional or anatomical bladder outlet obstruction, including posterior urethral valves and neuropathic bladders, than in children with primary VUR.[65] Lumping renal sequelae from all these pathophysiologic entities under the terms *renal scarring* or *reflux nephropathy* has hampered attempts at understanding the pathogenic mechanisms involved.

The critical role that infection plays in the pathogenesis of acquired renal scarring associated with reflux was clarified in Ransley and Risdon's classic experimental studies of VUR in piglets.[408] In the face of VUR and normal voiding pressures, renal scarring occurred only when urinary infection was present. In the absence of infection, renal changes only occurred when VUR was associated with increased bladder outlet resistance, so that obstruction, not reflux, was the pathophysiologic explanation for renal damage. Portions of the kidney at risk for scarring were those susceptible to pyelotubular backflow (intrarenal reflux) based on papillary morphology and configuration (Figures 7.20 and 7.21).

Clinically, new or progressive scarring is almost always associated with a history of UTI. Experimental studies and clinical experience have shown that even a single episode of pyelonephritis can lead to significant renal damage (Figure 7.22).[326,409] Furthermore, a clear association between the number of pyelonephritic attacks and incidence of renal scarring has been reported (Figure 7.23).[5,23,327,329] Both experimental and clinical studies have also shown that some renal scarring can be prevented or diminished by early antibiotic treatment of APN (Figures 7.24 and 7.25).[40,326,410,411] Conversely, a delay in antibiotic therapy is associated with an increased risk of DMSA scan–demonstrated APN.[412,413] Furthermore, when reflux is present, progressive renal scarring can be successfully prevented by

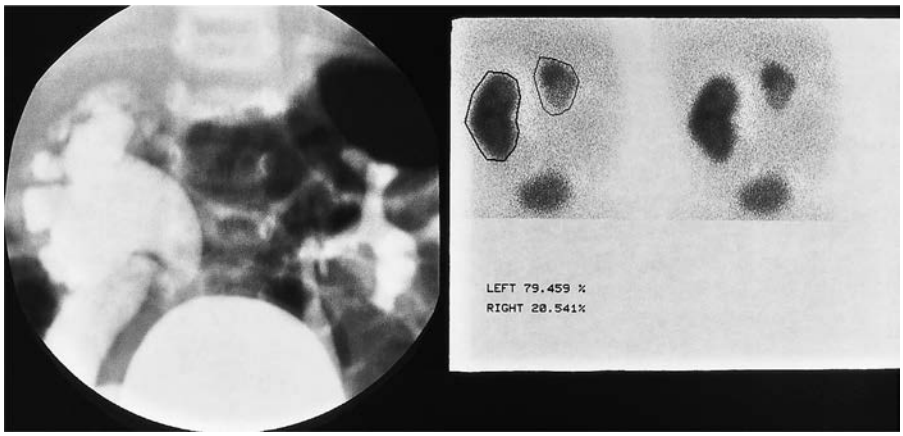

FIGURE 7.19 One-month-old boy with prenatally detected hydronephrosis. (*Left*) Voiding cystogram shows right grade V (note intrarenal reflux) and left grade III vesicoureteral reflux. (*Right*) ^{99m}Tc DMSA scan reveals a hypoplastic right kidney with markedly reduced differential renal function. He had been on antibiotic prophylaxis since birth and urine cultures were negative.

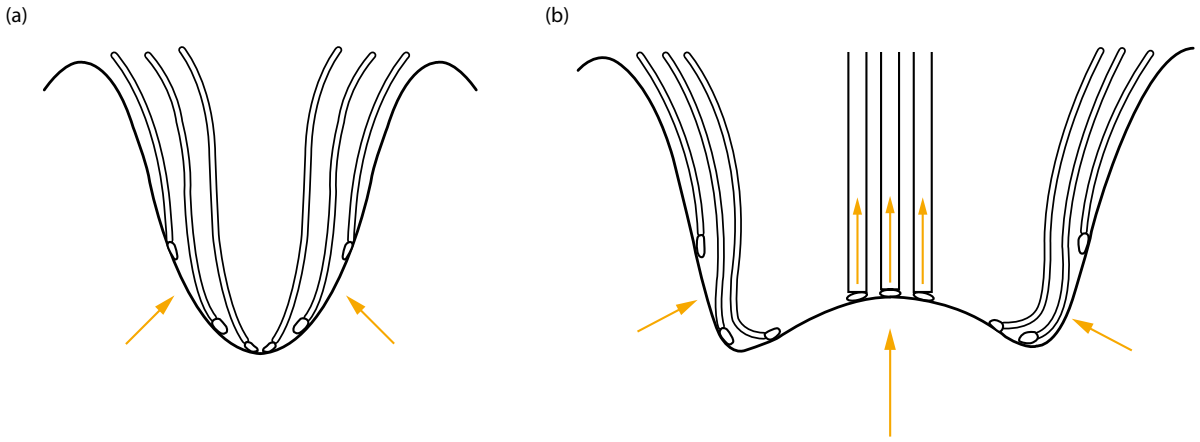

FIGURE 7.20 Papillary configuration in intrarenal reflux. (a) Convex papilla (non-refluxing): crescentric or slit-like orifices of collecting ducts opening obliquely onto the papilla. (b) Concave or flat papilla (refluxing papilla): round, gaping orifices of collecting ducts opening at right angles onto flat papilla. (Reprinted Ransley PG. *Part I. Urol Res* 1977;5:61. With permission.)

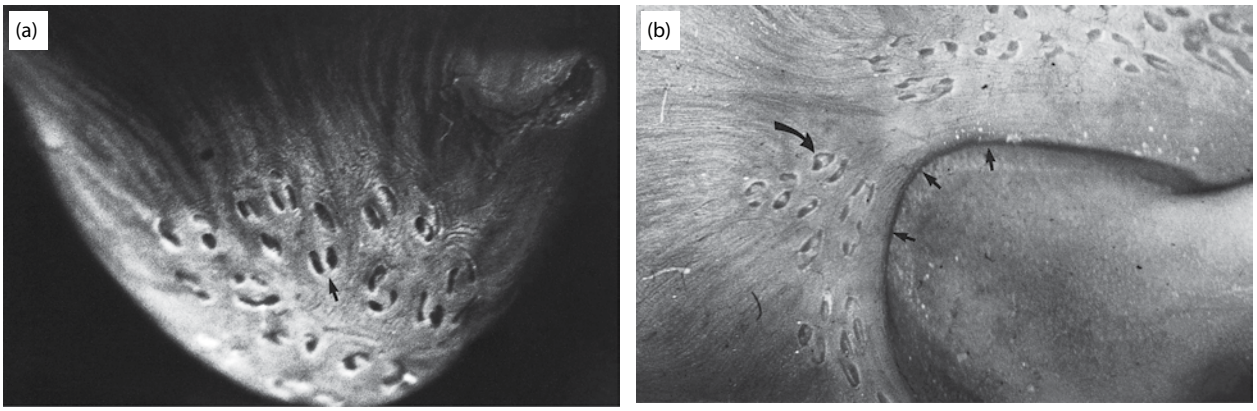

FIGURE 7.21 (a) Non-refluxing simple papilla with convex conical configuration and slit-like orifices of collecting ducts (arrow). (b) Refluxing compound papilla with concave configuration (arrows) and gaping oval to round orifices of collecting ducts (curved arrow). (Reprinted from Rushton HG et al. *J Urol* 1988;140:1169–74. With permission.)

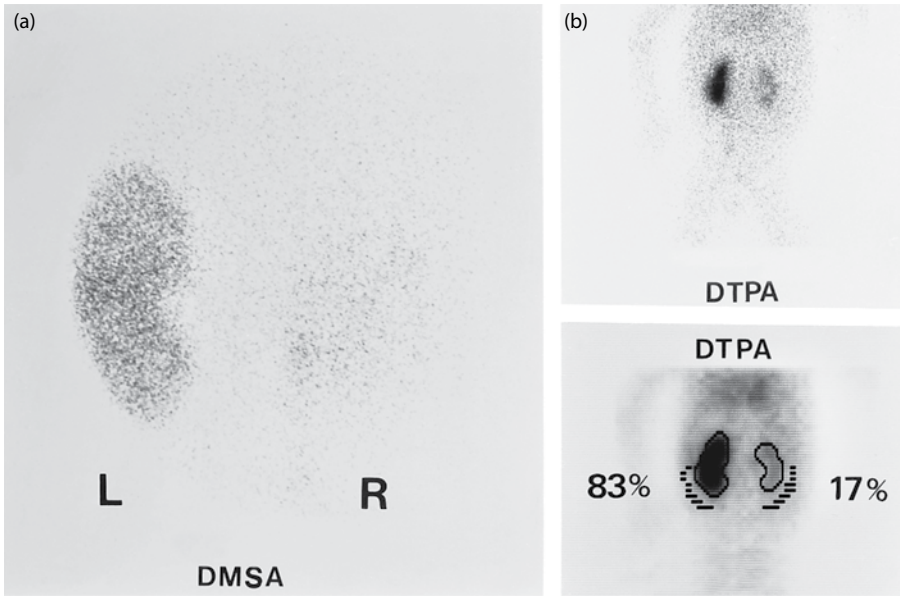

FIGURE 7.22 A 9-month-old girl hospitalized with her first febrile UTI. VCUG demonstrated right grade IV vesicoureteral reflux. Sonography showed moderate right hydronephrosis. (a) Initial ^{99m}Tc DMSA renal scan at the time of hospitalization demonstrates marked diffuse decreased uptake (function) in the right kidney, consistent with acute panpyelonephritis. (b) Follow-up ^{99m}Tc DTPA renal scan 1 month later shows partial recovery of function, but the kidney is contracted and scarred with a differential function of only 17%. (Reprinted from Rushton HG. Genitourinary infections: nonspecific infections. In: Kelalis PP, King LR, Belman AB, eds. *Clinical Pediatric Urology*, 3rd edn. Philadelphia: WB Saunders, 1992. With permission.)

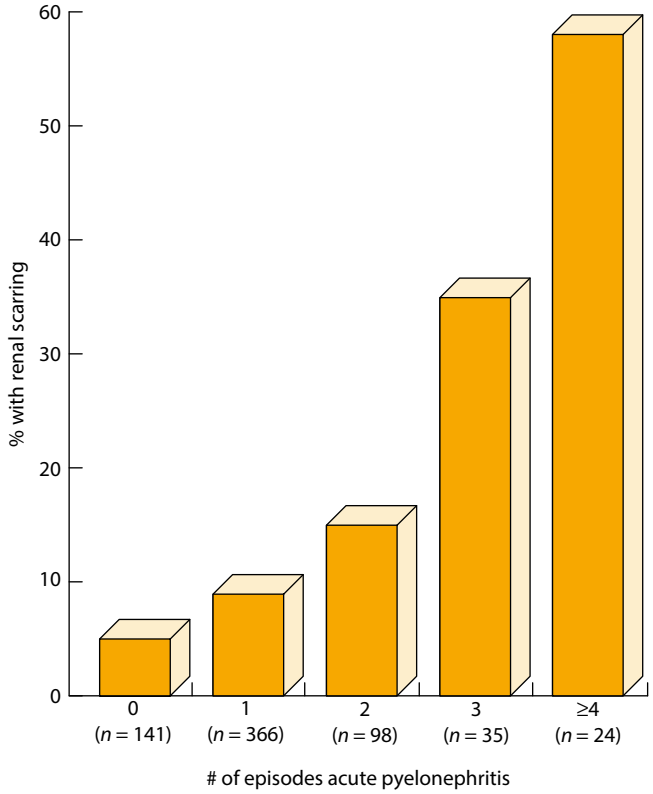

FIGURE 7.23 Relationship of renal scarring to number of episodes of acute pyelonephritis. (Adapted from Jodal U. *Infect Dis Clin North Am* 1987;1:713–29.)

keeping the patient free of infection.[400,401,414] Based on all the above, it is clear that infection, not reflux alone, is a prerequisite for acquired renal scarring.

Congenital reflux nephropathy associated with reflux

Severe reflux may be associated with significant renal dysplasia or hypoplasia thought to result from abnormal induction of the nephrogenic cord during embryogenesis.[415,416] Several reports have described DMSA scan renal functional abnormalities in patients with primary VUR detected prenatally.[402–406,417] The reported incidence of renographic abnormalities in these studies has varied widely, ranging from 17% to 60%.[402,403,405] Many of these infants were evaluated by renal scintigraphy prior to any known episodes of infection, confirming that the functional abnormalities present at birth represent a congenital abnormality of the renal cortex rather than one that is acquired. In one study, nephrectomy specimens in a few of these severely "scarred" kidneys with minimal function demonstrated severe dysplasia and growth arrest.[405]

Congenital reflux nephropathy is a pattern of impaired renal function and development that is particularly associated with high-grade VUR, especially males.[418] Mechanisms of developmental disruption are potentially related to VUR dynamics during gestation and associated bladder dynamics that continue into postnatal life. Congenital damage is often dysplasia that may be a result of disordered renal development secondary to significant alterations in bladder dynamics.[419] In other cases, the kidneys are hypoplastic but do not demonstate focal defects,

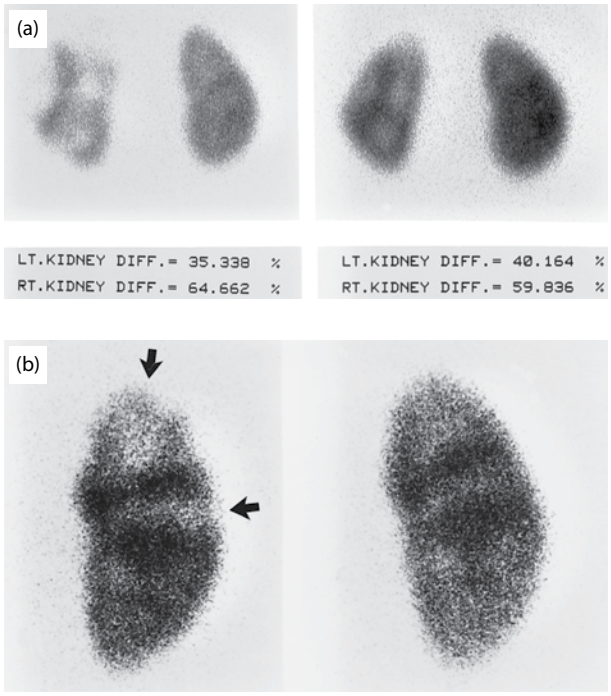

FIGURE 7.24 (a) ^{99m}Tc DTPA renal scan in a 3.5-year-old girl with left grade IV vesicoureteral reflux and multiple recurrent UTIs. (*Left*) Multifocal acute pyelonephritis is demonstrated in the upper and lower poles and midzone of the left kidney. (*Right*) Follow-up ^{99m}Tc DMSA renal scan 1 year later reveals significant improvement in function of the left kidney. (b) (*Left*) ^{99m}Tc DMSA renal scan in 4.5-year-old girl with acute pyelonephritis evidenced by typical changes of photopenia with preservation of the renal contour in the upper pole and mid-zone of the right kidney (arrows). (*Right*) Repeat DMSA renal scan 15 months later demonstrates complete resolution of acute inflammatory changes without residual scarring or loss of cortex. ([a] Reprinted with permission from Rushton HG. Reflux versus nonreflux pyelonephritis. In: Gonzales ET, Paulson DF, eds. *Problems in Urology. Advances in Pediatric Urology*, Vol. 8, Philadelphia: WB Saunders, 1994; [b] Reprinted from Rushton HG, Majd M. *J Urol* 1992;148(2 Pt 2):1726–32. With permission.)

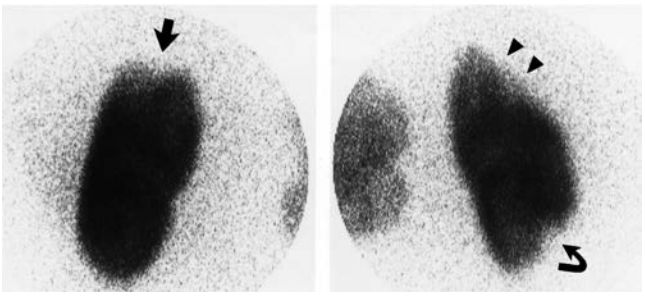

FIGURE 7.25 ^{99m}Tc DMSA renal scan in a 7-year-old girl 7 months after her first documented febrile UTI. A VCUG revealed bilateral grade II vesicoureteral reflux. Renal scarring is present in both kidneys. The left upper pole is flattened (arrow). There is a wedgeshaped defect in the right lower pole (curved arrow) and thinning of the right upper pole (arrowheads). (Reprinted from Rushton HG. Reflux versus nonreflux pyelonephritis. In: Gonzales ET, Paulson DF, eds. *Problems in Urology. Advances in Pediatric Urology*, Vol. 8, Philadelphia: WB Saunders, 1994. With permission.)

which may represent altered renal parenchymal development due to an abnormal or ectopic ureteral bud. In contrast, acquired damage associated with febrile UTI is the dominant etiology for renal scarring in girls.[420]

New or Acquired Scarring

Numerous studies have documented a link between UTI, VUR, and renal scarring with VUR considered to be a major risk factor for pyelonephritis and renal scarring.[421] Studies estimate that patients with high-grade VUR are 4–6 times more likely to have scarring than those with low-grade VUR, and 8–10 times more likely than patients without VUR.[329,345]

Until recently, a common assumption was that VUR was an absolute prerequisite for new or acquired renal scarring. This mind-set was further perpetuated by earlier investigations of new or acquired renal scarring, most of which focused retrospectively on patients with known VUR. However, in one earlier study that selected patients on the basis of infection alone, only half of the 37 children who formed new renal scars had VUR.[411] While the presence of VUR increases the risk of developing APN should UTI occur, thereby contributing to an increased risk of subsequent renal scarring, VUR by itself is not required for APN or for renal scarring.[63,422]

Several investigators have now evaluated the evolution of the acute inflammatory changes associated with pyelonephritis using serial DMSA renal scans.[351,423–426] The interval from the initial DMSA scan obtained at the time of acute infection until the repeat scan ranged from 3 months to 2 years. In one review, acute DMSA renal scan defects persisted as renal scarring in 36%–52% of kidneys.[389] The sites of new renal scarring corresponded exactly to those sites of APN seen on the initial DMSA renal scans, confirming the primary role of the acute inflammatory response to infection in the etiology of acquired renal scarring (Figure 7.26). Contralateral normal kidneys and initially uninvolved areas of abnormal kidneys have almost always remained normal on follow-up DMSA renal scans. Surprisingly, reflux has been present in only 25%–50% of kidneys that developed new renal scarring. This is attributable in part to the fact that the majority of patients (63%–75%) with acute inflammatory changes on the initial DMSA renal scans did not have VUR. In one prospective study of 38 kidneys with initially abnormal DMSA scans, scarring developed in 6 of 15 (40%) kidneys with associated VUR and in 10 of 23 (42%) kidneys without demonstrable reflux.[65] Similar findings have been observed by others.[427] These observations provide convincing clinical evidence that renal parenchymal infection, rather than VUR, is the prerequisite for acquired (postnatal) renal scarring.

Despite these findings, the importance of VUR (particularly grade III or higher) as a risk factor for renal scarring should not be discounted. In two meta-analyses of all studies published until 2009, the aggregate risk for renal scarring following APN as reported in the worldwide literature was sought. Studies performing sequential DMSA renal scans to identify APN and subsequent renal scars in children presenting with febrile UTI showed that the presence of VUR yielded a two- to threefold greater

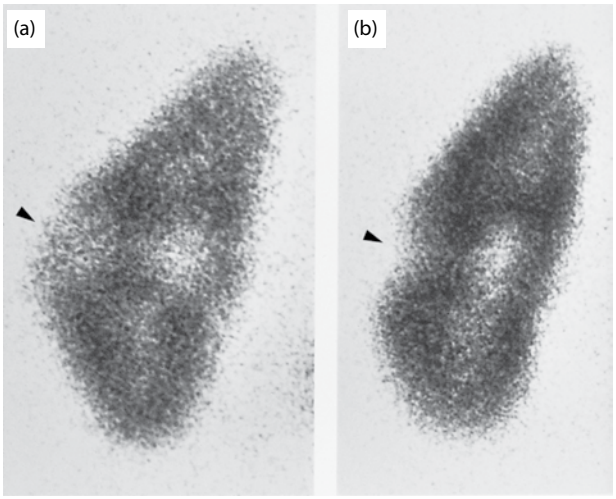

FIGURE 7.26 ^{99m}Tc DMSA renal scan in a 13-month-old girl with an acute febrile UTI. (a) Left posterior oblique view on the initial DMSA scan demonstrates acute pyelonephritis of the midzone of the left kidney evidenced by a photopenic lesion with preservation of the renal contour (arrowhead). (b) Follow-up DMSA renal scan reveals progression to renal scar in the exact same site characterized by contraction and loss of functioning renal cortex (arrowhead). (Reprinted from Rushton HG et al. *J Urol* 1992;147(5):1327–32. With permission.)

risk for renal scarring, and that children with grade III or higher VUR had a twofold greater risk of scarring than those with lower grades.[428,429] Although 62% of the kidneys with postpyelonephritic renal scarring in one study were drained by nonrefluxing ureters, renal scarring was still significantly more common in those kidneys with grade III or higher VUR than in kidneys with mild or no reflux.[427] Thus, the increased propensity for scarring in patients with higher grades of VUR is attributable in part to the increased risk of these kidneys for acute inflammatory damage at the time of the initial infection.[63,303,430] Coupled with this, reflux (pyelotubular backflow of urine from the pelvis into the collecting ducts) of infected urine or scarring of adjacent papillae may transform marginally competent, nonrefluxing papillae into papillae that do reflux, thereby predisposing the kidney to greater pyelonephritic damage.[63,408] Indeed, in one study that attempted to quantitate the area of acute pyelonephritic parenchymal damage, the presence of grade III or greater reflux was associated with a significantly greater frequency of kidneys demonstrating large defects (defined as >10% of the kidney demonstrating a DMSA uptake of <2 standard deviations of the control kidney) than kidneys with no VUR ($p < 0.02$).[430] Similarly, González et al. demonstrated that the risk of renal scarring affecting >25% of the kidney following DMSA-documented APN was 40% in patients with grades III and IV VUR compared with only 14% of those with grades I and II VUR and only 6% of those with no VUR.[431] Thus, when present, moderate or severe reflux (grade III or greater) remains the most significant host risk factor for APN and renal scarring.

Other risk factors for the development of renal scarring include associated bladder pathology, regardless of whether reflux is present. In one study, the frequency of new renal scarring was significantly higher in kidneys associated with overt bladder pathology than in those associated with normal bladders (86% vs. 32%, $p = 0.028$).[425] Yeung et al. evaluated 82 children with grades III or higher VUR. Those who had urodynamically proven abnormal bladder function were at significantly higher risk for development of breakthrough UTI and new renal scarring.[432] Urodynamic evaluation of children with neuropathic bladders associated with spina bifida has demonstrated that increased intravesical pressure may lead to upper tract deterioration, with or without VUR.[433] Animal studies have also shown an increased propensity for renal scarring when infection and reflux occur in the presence of bladder outlet obstruction.[408]

Two studies have also analyzed the association of various clinical and bacteriologic parameters with the development of new renal scarring.[425,427] In both, children who developed new renal scars were actually older at the time of APN, although the difference was statistically significant in only one.[426] An elevated WBC count at the time of the initial infection was not associated with renal scarring. When comparing those patients with and without new scarring, no significant differences were noted in race, gender, duration of fever, maximum temperature, or acute inflammatory signs (CRP or ESR) at the time of the acute pyelonephritic episode. *E. coli* was cultured from the urine of 88%–95% of the patients in both studies. Interestingly, new scarring occurred in 33%–41% of patients infected with *E. coli* compared with 100% of patients in both studies who were infected with other bacteria. In one study, no significant association was found between bacterial virulence factors (hemolysin, colicin, and P-fimbriae) and renal scarring, although colicin production was found almost twice as often in the bacteria isolated from patients with new renal scarring.[65] In a more recent report of 157 children evaluated with a DMSA renal scan 1 year following their first-time symptomatic UTI, children with high levels of CRP, high fever, and dilating VUR had an increased risk of renal scarring, up to 10 times higher than that of children with normal or slightly elevated CRP levels, no or mild fever, and no reflux.[350] Similarly, in a recent study evaluating serum PCT levels in patients with their first-time UTI, levels higher than 3.5 ng/mL were associated with an 18 times higher risk for renal scarring. Using a cutoff value of 2.0 ng/mL, an elevated PCT had a sensitivity of 97% and specificity of 66% for prediction of subsequent renal scarring.[258]

Imaging of Renal Scarring

In the past, the primary imaging modality for the detection of renal scarring was the intravenous pyelogram. However, limitations of IVP have actually hindered our understanding of the pathogenesis of renal scarring. Although relatively sensitive for the detection of renal scarring, IVP is not sensitive in the detection of APN.[308] Furthermore, pyelographic evidence of new renal scarring may take two or more years to develop after a documented UTI.[327,434] Consequently, this has forced investigators to speculate retrospectively about the etiology of renal scarring.

In contrast, DMSA renal cortical scintigraphy is capable of detecting the acute inflammatory changes of both

pyelonephritis and renal scarring. Several studies comparing the DMSA renal scan with IVP in the detection of renal scarring have demonstrated a greater sensitivity with isotope imaging, especially in younger children.[245,305,435–439] Merrick et al. compared the findings of IVP with those of DMSA scans in 79 children who had proven UTI and had been followed for a period of 1–4 years.[435] The sensitivity of IVP for the detection of renal scars was 80%, and the specificity was 92%, whereas cortical scintigraphy had a sensitivity of 92% and specificity of 98%. When both IVP and DMSA scintigraphy demonstrate scars, an excellent correlation on a site-by-site basis has been reported.[245,435–437,440] When compared with histology in an animal model, the sensitivity and specificity of the DMSA scan for the detection of renal scarring in 60 piglets with reflux and infected urine were 85% and 97%, respectively.[441] Studies that have compared ultrasonography with DMSA scintigraphy for the detection of renal scarring have consistently reported greater sensitivity with DMSA renal scans.[302,305,306] In one study, Yen and associates compared ultrasound, IVP, and both planar and SPECT DMSA renal scintigraphy in the evaluation of 130 children with UTI.[307] SPECT imaging of DMSA scans detected the highest number of defects, followed by planar imaging. Thus, DMSA renal cortical scintigraphy offers a superior opportunity to study the progression of renal damage or functional loss from the time of the initial insult until either complete healing or irreversible scarring develops.

Renal scars detected by DMSA scintigraphy appear as focal or generalized areas of diminished uptake of radioisotope associated with loss or contraction of functioning renal cortex. This may appear as thinning or flattening of the cortex in some kidneys, while in others, renal scars appear as classic discrete wedge-shaped parenchymal defects (Figure 7.27). In more severe cases, generalized damage may be associated with multifocal or diffusely scarred kidneys and reduced differential renal function. In contrast, defects associated with APN are more typically characterized by focal areas of diminished uptake but with preservation of the normal renal contour (Figure 7.26). Although it is often possible for an experienced observer to distinguish acute versus chronic lesions, it should be recognized that this differentiation may be less apparent in those kidneys with APN superimposed on preexistent renal scarring.

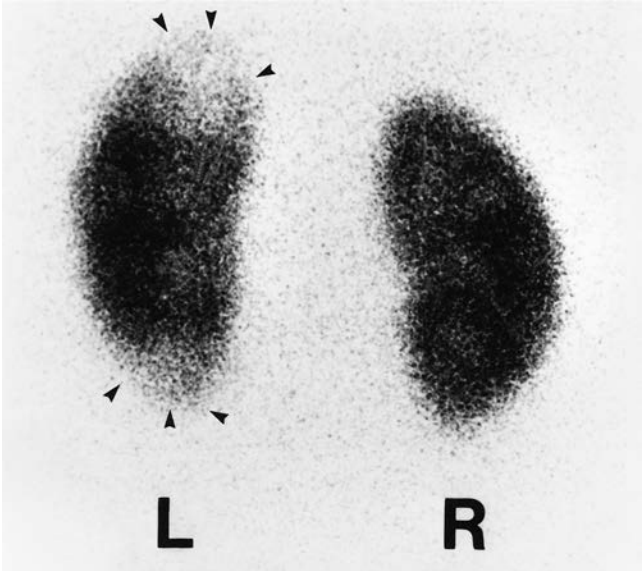

FIGURE 7.27 ^{99m}Tc DMSA renal scan demonstrates typical changes of acute pyelonephritis in the upper and lower poles of the left kidney. Diminished uptake of isotope is seen with an intact renal cortical outline without volume loss or contraction (arrowheads). (Reprinted from Cohen RA et al. *J Urol* 1990; 144:541–54. With permission.)

Sequelae of Renal Scarring

Hypertension

Renal scarring has been reported to be a common cause of hypertension in children and young adults.[440–443] The risk of hypertension in patients with renal scarring varies, based on length of follow-up and severity of scarring. In follow-up studies of children with renal scarring, approximately 6%–13% of children with scarring will develop hypertension.[23,231,446–448] In some cases, it may be associated with progressive renal insufficiency.[449] A report of an older cohort of 294 patients (mean age at presentation of 17.3 years) with reflux nephropathy noted that the risk of hypertension increased with age and length of follow-up.[450] Whereas 8.5% of these patients had hypertension at presentation, 38% became hypertensive later on (mean age 34.2 years). Hypertension was significantly more common in those with severe bilateral parenchymal scarring. Similarly, in another series, 13% (11/83) of children with renal scarring were hypertensive at initial evaluation and another 17% (14/83) developed hypertension over the subsequent 4–20 years.[451]

The development of hypertension is clearly related to the severity of renal scarring and is more often observed in patients with a history of recurrent episodes of pyelonephritis associated with moderate or severe VUR.[231,449] The actual risk for hypertension in children with milder degrees of scarring is unknown, but is undoubtedly much less. The etiology of hypertension associated with renal scarring is controversial. Some investigators report no evidence that the renin–angiotensin–aldosterone (RAS) system contributes to this, while others report that it does.[452–457] Despite these controversies, most would agree that the risk for hypertension in patients with severe renal scarring is significant, and long-term follow-up is mandatory, since hypertension may take 10–20 years to develop.

Renal Insufficiency

The actual risk of renal insufficiency secondary to post-pyelonephritic renal scarring is unknown. The annual incidence of new patients presenting with end stage renal disease (ESRD) associated with "reflux nephropathy" in Australia and New Zealand between 1985 and 1989 was 3.9 and 4.89 per million of the population, respectively.[458] Overall, this represented 7% of all new cases of ESRD commencing treatment during this time period, including 24% in the teenage group. In a more recent study of 102 patients with ESRD seen at a pediatric hospital over a 10-year period, only 3 had reflux nephropathy, including

1 patient with no history of UTI and another with a single, afebrile UTI.[459]

Studies have shown that the incidence of renal insufficiency in patients with postpyelonephritic renal scarring increases with age. The incidence of renal insufficiency in a report by Martinell et al. of 30 adults who were diagnosed with severe renal scarring as children was 10%.[23] Another study of an older cohort of 294 patients (mean age at presentation of 17.2 years) with reflux nephropathy found a 2% incidence of renal insufficiency (defined as GFR of <40–69 mL/min) at presentation, which increased to 24% at last follow-up (mean age 34.2 years). The more extensive the renal scarring, the higher the proportion with renal insufficiency.[449] Most patients (90%–100%) with reflux nephropathy and ESRD have focal segmental glomerulosclerosis, almost always associated with proteinuria.[460–463]

TREATMENT

The obvious goals of treatment of UTI are symptomatic relief and prevention of new or progressive renal damage, especially in infants and young children who are at greatest risk for renal scarring. Initial treatment, ideally, should be based on in vitro sensitivity studies. Frequently, such testing is not done or treatment is instituted before the results are available. Fortunately, because the common uropathogens are susceptible to multiple antibiotics and the response to antibiotics correlates best with urine levels that are usually more highly concentrated than serum levels, high cure rates have been reported in most therapeutic trials.[464]

Asymptomatic Bacteriuria

Treatment of true ABU does not appear to be necessary if the urinary tract is otherwise normal.[376,465,466] The risk for pyelonephritis in infants and young girls with untreated ABU is small, and many demonstrate spontaneous remission.[5,17] In a prospective follow-up of 50 infants with initial screening bacteriuria, 37 were followed for a minimum of 6 years.[467] Of the original 50, 2 infants developed pyelonephritis within 2 weeks of bacteriuria being diagnosed. In 45, bacteriuria was left untreated. Spontaneous clearance was observed in 36, while in 8 clearance followed treatment with antibiotics for respiratory infections. Recurrences of bacteriuria were observed in 10 of 50 children, of whom one had pyelonephritis. No child had more than one recurrence. Follow-up urography in 36 of 50 children after a median of 32 months showed no evidence of renal damage in any.

In contrast to infants with screening bacteriuria, treatment of school-aged girls with ABU is followed by high recurrence rates of up to 80%.[11] Most are caused by new strains, which may carry the risk of being more virulent.[468,469] In contrast, when ABU is left untreated, spontaneous changes of strain are uncommon.[470]

Several studies in the 1970s reported that nontreatment of ABU was associated with normal growth of kidneys without the development of new scars provided the urinary tract initially appeared normal radiographically.[14,283,285,286] In a 4-year follow-up by the Cardiff-Oxford Bacteriuria Study Group in children 5–12 years of age with untreated covert bacteriuria, new or progressive renal scarring did not occur unless VUR was present.[286] Similarly, the presence of ABU in the absence of VUR is not a risk factor for renal scarring in children with neuropathic bladders who perform clean intermittent catheterization.[378]

Hansson et al. retrospectively compared treatment with nontreatment of ABU in older girls (median age 8 years) with preexistent renal scarring.[471] Many also had mild grade I or II/V VUR. Of 21 girls who were given a short course of antibiotics, 17 acquired a new infection within a year, including 7 with pyelonephritic recurrences. Of 23 girls treated with antibiotic prophylaxis for 2–3 years, one-half developed breakthrough infections, and recurrences after completion of long-term prophylaxis were as common as after short-term treatment. Overall, in girls who received short- or long-term antibiotic treatment, 14 patients developed 21 episodes of APN during a total of 140 patient-years of observation. In contrast, ABU was left untreated in 29 girls for a total of 74 patient-years of observation. Only one patient developed APN.

Based on this information, it is reasonable that true ABU, particularly in older girls, be left untreated.[129,286] However, in the presence of VUR, the risks of nontreatment of ABU have not been clearly established, particularly in infants and younger children. It should also be recognized that bladder dysfunction is commonly found in girls with so-called ABU, including detrusor instability and incomplete emptying.[204] This explains in part the marked tendency for recurrent infection after treatment of ABU with antibiotics alone. Treatment of the underlying voiding dysfunction is key to the successful long-term management of these patients.

Uncomplicated Lower Urinary Tract Infection

Agents that have been used successfully for acute, uncomplicated lower urinary infections include sulfonamides, trimethoprim-sulfamethoxazole (TMP-SMX), nitrofurantoin, TMP, and oral cephalosporins (see the appendix). Unfortunately, ampicillin and amoxicillin are used commonly by primary healthcare physicians. High intestinal levels of these two antibiotics often result in rapid development of resistant enteric organisms, which then become the reinfecting bacteria. The emergence of resistant strains to ampicillin or amoxicillin has further limited its initial efficacy in treating urinary infections compared with other antibiotics.[472] Resistance rates to ampicillin or amoxicillin have been reported to be as high as 54% in children with their first documented symptomatic UTI.[473] This drawback of the synthetic penicillins has been diminished by the relatively recent combination of clavulinic acid with amoxicillin (Augmentin®). Clavulinic acid inhibits the bacterial β-lactamase enzymes, which render the β-lactamic antibiotics ineffective. This combination has proved effective in eradication of UTIs in children, even when in vitro susceptibility testing demonstrated resistance to amoxicillin alone.[474,475] However, ampicillin–clavulinic acid is associated with a high incidence of side effects, is expensive, and is no more effective than the

usual drugs. Increasing resistance to TMP-SMX has also been reported over the last decade.[368]

The fluoroquinolones have been shown to have a wide spectrum of activity that includes most gram-positive and gram-negative organisms, including *Pseudomonas aeruginosa* and *Proteus*.[476] However, concern regarding adverse arthropathic effects, based on animal studies showing cartilage toxicity, has prevented its approval for routine use in children.[477] However, the same experimental toxic effects have been reported with all quinolones, including nalidixic acid, which is licensed for use and has been used in children for decades.[478] A retrospective match-controlled study of nalidixic acid in 11 children treated for 10–600 days with follow-up examination 3–12 years later did not reveal any differences in arthropathic adverse effects compared with controls.[479] Furthermore, clinical evidence of cartilage toxicity has not been reported in more than 100 children with cystic fibrosis treated with varying courses of high-dose ciprofloxacin.[480] Currently, Cipro fluoroquinolone has received Food and Drug Administration (FDA) approval for the treatment of complicated UTIs in children.[481]

Several randomized controlled studies have been published reporting the efficacy of single-dose or short-course antimicrobial therapy for treatment of uncomplicated lower UTIs in children. The potential advantages of short-course therapy include decreased costs, improved compliance, decreased antibiotic-related side effects, and decreased effect on the fecal flora.

In 1988, Moffatt and associates reported a methodological analysis by four independent reviewers of 14 randomized controlled trials of short-course antimicrobial therapy for uncomplicated lower UTIs in children. Short-course therapy varied in these 14 studies. Conventional therapy ranged from 7 to 10 days. In two of the studies, short-course therapy was less effective.[482] One study compared single-dose with 10-day amoxicillin therapy and one compared 1-day with 10-day cefadroxil therapy.[483,484] The other 12 studies showed no difference in outcome. The authors concluded that there was still insufficient evidence to recommend short-course therapy for UTIs in children.

In a subsequent review article published by Khan, the findings in 12 of these reports were reevaluated by pooling the data on 320 infants and children.[485] He reported that single-dose therapy achieved an overall cure rate of 89% (63%–100%), defined as a negative follow-up culture at 1 week and the lack of a subsequent recurrence with the same organism. However, the response varied with the antimicrobial agents. Intramuscular aminoglycosides, used in 178 infants and children (56%), achieved the highest cure rate (96%), followed by TMP-SMX or a sulfa drug (90%). The cure rate of amoxicillin was significantly less (75%, $p < 0.01$). Another large clinical study investigated single-dose versus multidose antibiotic therapy in 132 children with a culture-documented "first-time" acute UTI. There was no difference in the bacteriologic cure rate for single-dose (93%) versus multidose regimens (96%), but recurrence rates at 10–12 days or 28–37 days after treatment were significantly higher in the single-dose group (20.5%) than in the 3-day (5.6%) and 7-day (8%) groups.[486]

Two other studies have compared relatively short 3-day with conventional 10-day courses of antibiotics for treatment of uncomplicated UTIs in children. In one prospective, randomized, open multicenter study of 264 girls, 1–15 years old, similar results were observed when short-course treatment with 3 days of either sulfamethizole or pivmecillinam was compared with 10 days of sulfamethizole.[487] Specifically, there was no difference in the number of girls with no or insignificant growth on urine cultures after treatment or in the recurrence-free interval after treatment among the three groups. In another study of 110 children, no difference in initial cure or subsequent relapse rates was found in children treated with 3-day therapy versus 10 days using either cotrimoxazole or nitrofurantoin.[488]

Based on the available data, it appears reasonable to treat acute lower uncomplicated infections in children with a relatively short 3-day course of antibiotics.

Pyelonephritis

The child with suspected pyelonephritis requires a greater degree of assurance of immediate therapeutic success, since the degree of scarring and renal damage resulting from an infection may be influenced by the rapidity of effective therapy.[40,326,410–413,489] Oral medication can be initiated in older children who are not septic or vomiting as long as good compliance is ensured. TMP-SMX can be anticipated to be effective in most cases. Cephalosporins are also a good choice for initial therapy in the febrile child who does not require parenteral therapy. Third-generation cephalosporins, such as cefixime, offer the advantage of once-daily dosing and have been shown to be as effective as twice-daily TMP-SMX.[490,491] Treatment can be changed to include less expensive agents when the antibiotic sensitivities become available.

There is controversy over the need for hospitalization and treatment with parenteral antibiotics versus outpatient therapy with oral drugs. However, in a prospective randomized clinical trial of 306 children 1–24 months old with febrile UTIs, outpatient treatment with oral third-generation cephalosporins was equally effective when compared with initial treatment with intravenous antibiotics. There was no significant difference in treatment success, duration of fever, or subsequent renal scarring on DMSA scans.[491] Not surprisingly, costs for treatment of children were significantly higher for those treated with intravenous antibiotics.

Clearly, there is a need for more controlled therapeutic trials for febrile UTI in children with old and new drugs in different dosages and for varying lengths of treatment. Ideally, these trials should categorize patients into different age groups, such as (1) neonates aged 0–28 days, (2) infants aged 1 month to <2 years, (3) older children of ≥2 years, and (4) adolescents.[492] Meanwhile, until such clinical trials are conducted, nontoxic children and infants of >2 months of age can be treated as outpatients as long as compliance is not an issue. It is also reasonable to initiate therapy with 1–2 days of a long-acting, third-generation cephalosporin, such as ceftriaxone, administered intramuscularly, followed by 10–14 days of oral antibiotics and prophylaxis until

evaluated. Ceftriaxone is active against most gram-negative uropathogens, and it achieves very high levels in both the urine and renal parenchyma following single daily doses.[493] This approach virtually ensures compliance and adequate antimicrobial coverage until the urine culture and sensitivity results are known. Alternatively, if compliance does not seem to be a problem, initial therapy with appropriate, broad-spectrum oral antibiotics may be as effective in the treatment of APN and in the prevention of irreversible renal damage.[491]

In contrast, the toxic child and infants of <2 months of age with suspected APN should be considered candidates for hospitalization and parenteral therapy. Typically, one of the newer third-generation cephalosporins may be used, but these do not provide comprehensive coverage of gram-positive organisms, including enterococcus. Parenteral antibiotic therapy should be continued for 5–7 days in neonates, although oral outpatient therapy to complete a full 10- to 14-day course can be substituted in patients of >2 months when afebrile for 24–48 hours. Follow-up specimens for urine culture should be obtained at the completion of therapy, and prophylaxis should be instituted until evaluation of the urinary tract is completed. In addition, circumcision may be considered in patients with higher grades of VUR and a history of febrile UTI based on the increased risk of UTI.

Dysfunctional Elimination

In addition to appropriate antimicrobial therapy, other factors must be taken into consideration in patient management. Voiding frequency and control of constipation are the two most common variables that are readily changeable and may be the most important in effecting changes in susceptibility to infection, particularly for children who are infrequent voiders. Establishing a voiding schedule in children may be extremely difficult and may provoke conflict in the parent–child relationship. The physician can interject his or her influence by explaining the treatment goal to the child and requesting that a regular voiding pattern be instituted and maintained. The child should be told that he or she will be reminded by his or her parents to void regularly, and that he or she should follow this request even if he or she does not feel the urge to void at that time. Multialarm wristwatches can be a useful and inexpensive reminder for older school-aged children.

The mainstay of treatment of children with recurrent UTIs and underlying bladder instability often involves the long-term use of anticholinergic medicine, primarily oxybutynin (Ditropan). Other anticholinergic and antispasmodic agents include hyoscyamine (Levsinex) and tolterodine (Detrol). Koff and Murtagh reported that after initial clearing of urinary infection, 31 of 58 (58%) children with recurrent UTIs and uninhibited bladder contractions who were treated with anticholinergics alone maintained sterile urine. The necessity for long-term antibiotic prophylaxis in these patients is then determined by the frequency of subsequent recurrences and/or the presence of VUR.[494] For children older than 6 years, the usual dosage of oxybutynin is 2.5–5 mg, given two to three times daily. A long-acting formulation, Ditropan XL, is available that only requires once-daily dosing. The usual dose for hyoscyamine in this age child is one 0.375 mg time capsule twice daily. Although not yet approved for children, tolterodine has been used successfully with doses of 1–2 mg twice daily. Reportedly, tolterodine has a more specific action on the bladder and is associated with fewer side effects. Comparative efficacy among these medications has not been established in children. Timed voiding should always be used in conjunction with anticholinergic therapy. Therapy directed toward associated constipation should always be initiated prior to starting treatment with intravenous anticholinergics.

In more difficult cases of voiding dysfunction with detrusor sphincter dyssynergia, pelvic floor relaxation biofeedback therapy has been used successfully in the treatment of recurrent UTIs.[495] In a report, 42 girls with recurrent UTIs and urodynamically confirmed dysfunctional voiding were treated with a multimodal approach involving pelvic floor relaxation biofeedback, a voiding and drinking schedule, anticholinergics in those with bladder instability, and antibiotic prophylaxis.[213] This combined therapeutic approach was effective in preventing recurrent UTIs in 35 girls (83%).

For constipation, an intensive therapeutic approach is often required. Increased intake of fiber and fluid and regular toilet habits must then be instituted. In refractory cases, regular use of a fiber-based laxative may be necessary. Initially, in severe cases, enemas given for several days may be necessary to disrupt a high fecal impaction and relax an overstretched colon. In most cases, the continuation of a bowel or bladder regimen is a long-term requirement, and failure to comply with this regimen generally results in recurrence of both constipation and UTI.[496] However, successful management can result in significant improvement in voiding dysfunction and a reduction in recurrent UTIs. A recent study of 234 constipated and encopretic children found that urinary infection was present in 11%, daytime urinary incontinence in 29%, and nocturnal incontinence in 34%.[213] During follow-up of at least 12 months after initiation of treatment for constipation, recurrent UTIs were effectively prevented in all patients who had no anatomic abnormality of the urinary tract. Daytime urinary incontinence resolved in 89% and nocturnal incontinence resolved in 63% of patients.

Urinary stasis for any other reason needs to be addressed if infection cannot be otherwise controlled with antibiotic prophylaxis. Wenske et al. have demonstrated that α-blockers are effective in decreasing postvoid residuals in children with primary bladder neck dysfunction.[497] Other causes of urinary stasis may include severe reflux with secondary poor bladder emptying (megacystis–megaureter syndrome), dilatation in the absence of obstruction, bladder diverticula, or residual ureteral stumps. Since otherwise unexplained urinary infection is so common, it is incumbent upon the physician to document the influence of any of these entities on infection prior to recommending surgical correction. For example, a specimen for culture may be obtained by needle aspiration of a dilated, nonobstructed upper collecting system to ascertain its involvement prior to surgical revision.

Renal Abscess

In the past, the majority of renal abscesses, a rare form of renal infection, were not thought to be the result of ascending infection. Historically, *Staphylococcus aureus* was the offending agent, resulting from hematogenous seeding from a peripheral cutaneous site of origin.[498,499] Diagnosis was often delayed in these patients because urine cultures are negative in most. With the advent of early recognition and effective therapy, the frequency of staphylococcal bacteremia and renal abscesses has decreased. More cases of gram-negative infections in the presence of VUR or other anatomic abnormalities of the urinary tract are now being seen.[500]

Most patients with a renal abscess present with high fever, leukocytosis, and an elevated ESR, often accompanied by flank pain. A variety of imaging techniques have been used to diagnose renal abscesses, including gallium-67 scintigraphy, sonography, and CT (Figure 7.28).[501–505] The classic treatment of renal abscess has been surgical drainage, in addition to appropriate antibiotic therapy. However, improved antibiotics and diagnostic techniques, together with the ability to obtain culture by percutaneous aspiration or drainage under ultrasonic control, have often obviated the necessity for surgical intervention. In seven patients reported by Schiff et al., 10 days of parenteral antibiotic treatment alone, followed by an additional 2 weeks of appropriate oral therapy, was successful.[506] However, in a review of the literature performed by Steele et al., 62% (16/23) of the children with renal abscesses ultimately required surgical intervention.[507] Unfortunately, in part due to the rarity of this type of infection, no controlled data exist that rigorously compare the resolution rate between children treated with antibiotics alone and those treated with antibiotics and drainage. Currently, many cases of renal abscess initially can be managed without intervention, with percutaneous drainage being reserved for persistent infection (Figure 7.29). Children who are immunocompromised by virtue of malnutrition or infection with the human immunodeficiency virus (HIV) are at particular risk for developing recurrent renal abscesses and abscesses containing unusual organisms (*Listeria monocytogenes*).[508,509] In these circumstances, more aggressive surgical or percutaneous intervention is often necessary early to eradicate the infection.

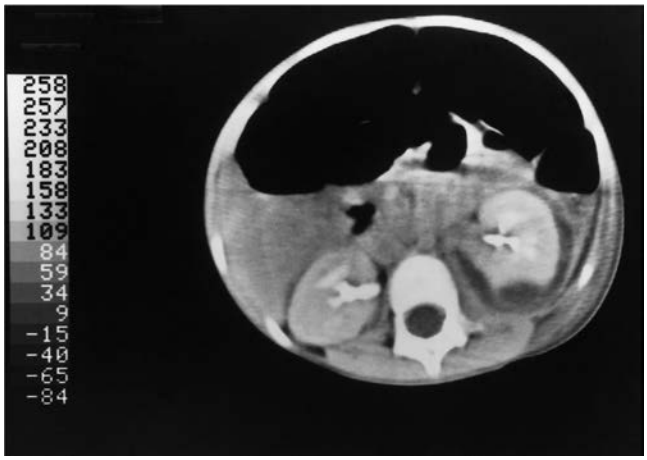

FIGURE 7.28 CT scan reveals a filling defect in upper pole of left kidney consistent with a renal abscess in a child with flank pain and fever. (Reprinted from Rushton HG. Genitourinary infections: nonspecific infections. In: Kelalis PP, King LR, Belman AB, eds. *Clinical Pediatric Urology*, 3rd edn. Philadelphia: WB Saunders, 1992. With permission.)

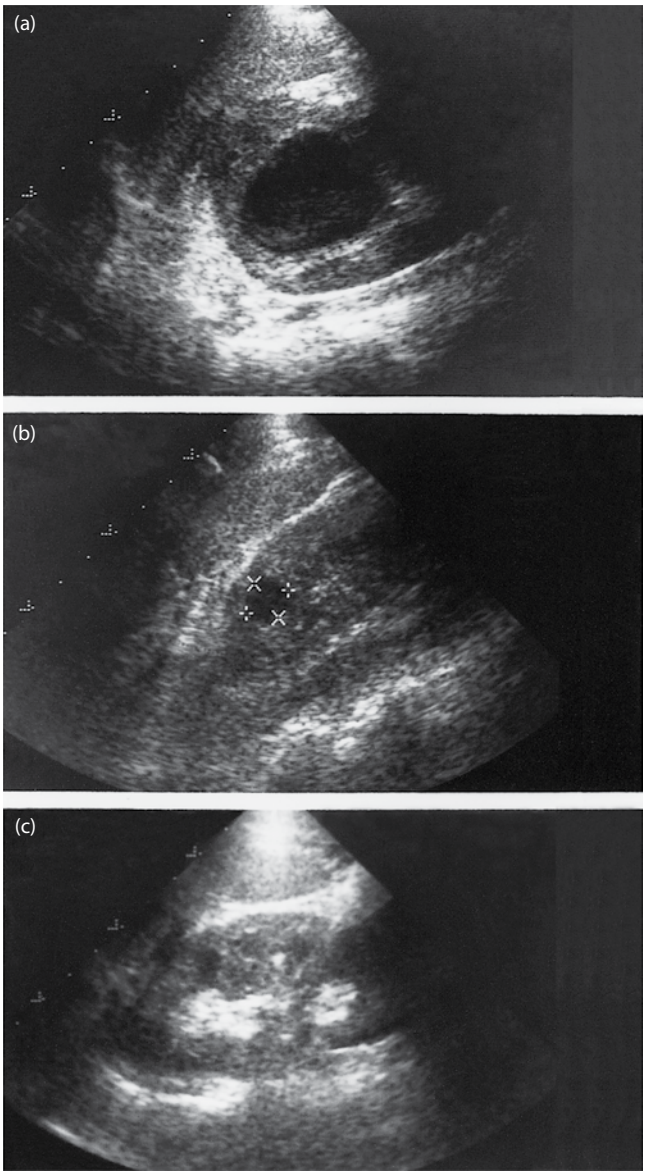

FIGURE 7.29 Sonogram in a 16-year-old girl who presented with fever and flank pain. (a) Sonolucent mass in the left upper pole consistent with a renal abscess. Needle aspiration under sonographic guidance yielded purulent material that grew *E. coli*. Following 2 weeks of parenteral and 4 weeks of oral antibiotic therapy, sonograms 7 weeks later (b) and 17 weeks later (c) show progressive resolution of abscess cavity. (Reprinted from Rushton HG. Genitourinary infections: nonspecific infections. In: Kelalis PP, King LR, Belman AB, eds. Clinical Pediatric Urology, 3rd edn. Philadelphia: WB Saunders, 1992. With permission.)

Xanthogranulomatous Pyelonephritis

Xanthogranulomatous pyelonephritis is an atypical form of severe chronic renal parenchymal infection characterized by unilateral destruction of parenchyma and accumulation of lipid-laden macrophages (xanthoma cells) either surrounding abscess cavities or as discrete yellow nodules. More than 50 cases of xanthogranulomatous pyelonephritis have been reported in children.[496,510,511] The age of presentation has ranged from infancy to 16 years. Most patients present with nonspecific symptoms of chronic infection, including weight loss, recurrent fever, failure to thrive, pallor, and lethargy, although those with the focal form often appear healthy.[496,510] A palpable abdominal mass is present in approximately one-third of cases. Bacterial specimens for culture can be obtained from the urine or renal abscess in the majority of cases, with *Proteus* being the most common organism isolated.

Both diffuse and focal forms of the disease have been reported, with the focal form being more common in children than in adults.[510,512] The pathologic and radiologic differences between focal and diffuse xanthogranulomatous pyelonephritis have been described.[513] Radiologic evaluation in the diffuse form of the disease often reveals nonfunctioning of the entire kidney. Calcification or stones may be present, although this is less common in the focal form of the disease. Characteristic sonographic or CT appearances of xanthogranulomatous pyelonephritis also have been reported.[514] However, these features are nonspecific and often mimic neoplasia or other forms of chronic inflammatory renal parenchymal disease. Consequently, the correct diagnosis is seldom made preoperatively.[515] Nephrectomy is curative, although partial nephrectomy may be adequate in focal disease, assuming that the diagnosis can be established. No incidence of recurrence in the contralateral kidney has been reported.

Tuberculosis

Genitourinary tuberculosis (TB) is a form of secondary TB and is rare in children. Historically, it presents 1–5 years after initial infection.[516] It is more prevalent in non-Westernized populations, where TB is still endemic in many countries. It is important to be considered, however, in patients with immune deficiencies. Genitourinary TB most commonly presents in children with symptoms of lower UTI; however, mycobacterium is rarely identified on urine culture.[516]

Research in South Africa has investigated the renal effects of patients with coinfection of HIV and TB given the endemic presence of both diseases. The classical presentation of renal TB is kidney damage from obstruction or massive casseous destruction.[517] In this studied population, the presentation was granulomatous TB interstitial nephritis with renal function impairment and proteinuria. They concluded that TB can contribute to proteinuria and renal disease in children with HIV if they are not treated with antitubucular medications.[517]

The mainstay of genitourinary tuberculosis (GUTB) treatment is antimycobacterial chemotherapy, with surgical resection limited to patients with nonfunctioning kidney or recurrent infections.[518] Unroofing of renal abscess is no longer recommended when interventional radiology is present with the ability to drain the abscess percutaneously. Stricture disease and bladder fibrosis must also be managed appropriately. In children, this often means ureteral reconstruction for prevention of long-tern stricture complication and reoperations.[519] Isoniazid, pyrazinamide, ethambutol, and rifampicin in combination are the medications of choice. The time frame for treatment varies depending on the extent of disease. No randomized control trials have investigated the optimal duration of treatment for GUTB. Many recommendations include an "intense phase" with use of all four drugs for 2 months, followed by a "maintenance phase" of rifampicin and isoniazid for 4 months.[518] There is a rise in multi-drug-resistant TB associated with poorly managed pharmacotherapy, and many countries now utilize directly observed therapy to reduce the risk of drug resistance.

Treatment in Renal Failure

The dynamics of antibiotic detoxification and excretion are usually deranged in the child with renal failure. Antibacterial doses need to be adjusted in such patients to avoid adverse reactions. Certain drugs, those that are dependent on renal function for efficacy, are useless in these patients. The frequency of administration of those drugs that are effective in the face of renal failure, rather than their dosages, should be modified based on the degree of renal insufficiency.

Resistance

Negative selection imposed on the normal beneficial gut mircobiota by antibiotics may ultimately change the healthy state of the individual, resulting in an increased risk of opportunistic or recurrent infections.[520] More than 15 million women suffer from UTI annually in the United States, with estimated costs exceeding $2.5 billion.[521] UPEC is the causative agent in more than 85% of all UTIs, which are becoming more difficult to treat with increasing antimicrobial resistance to standard of care therapy and high recurrence rates leading to increased cost and a rise in multiresistant strains.[521] At this time, numerous groups are investigating possible molecular causes for increased bacterial resistance.[522–527] In the future, it may be possible to prevent and restrict resistance patterns in populations before they are endemic.

Antibiotic Prophylaxis

Long-term, continuous antibiotic prophylaxis has been recommended in children with a history of UTI and VUR (particularly under 5 years of age) and those with frequent symptomatic recurrences of UTI even in the absence of VUR. There are also children with prenatal hydronephrosis or a strong family history of VUR who are identified to have grades III–V VUR in whom antibiotic prophylaxis is recommended, particularly for those infants under 1 year of age.[201]

In the past, prophylaxis was usually continued in children with VUR until the reflux spontaneously resolved

or was surgically corrected. Some now advocate stopping prophylaxis in children older than 5 or 6 years of age who have mild or even moderate (grades I–III) VUR, particularly when there is no evidence of prior renal scarring.[528,529] If infection recurs during that time and reflux persists, correction should be considered for those with clinical or DMSA scan–documented pyelonephritis. Regardless of whether reflux is present, girls with a history of recurrent UTIs should be advised of the importance of surveillance urine cultures during pregnancy because they are at increased risk for pyelonephritis. In one review, a group of 41 women who had UTIs in childhood were followed through 65 pregnancies.[22] They were compared with age-matched controls. Of those with a history of childhood UTIs, 19 had renal scarring and 22 did not. The incidence of bacteriuria was higher in those with renal scarring (47%) than in those without renal scarring (27%), but both were significantly greater ($p < 0.001$ and <0.01, respectively) than in controls without a history of UTI (2%). This is true regardless of whether reflux is present.[21] Even those who undergo successful surgical correction of reflux during childhood may continue to be at increased risk for pyelonephritis during pregnancy.[530–532]

Children with recurrent pyelonephritis and those with frequent recurrent symptomatic lower UTIs (three in 6 months, four in a year) should also be considered for prophylaxis for a minimum of 6–12 months, even in the absence of VUR. Periodic urine specimens for culture should be obtained every 3–6 months to monitor the success of prophylaxis. Medication should then be reinstituted for an additional 12 months if infection recurs within 3 months of discontinuation. It is not necessary to discontinue treatment to obtain urine specimens for culture. When breakthrough infection occurs, the offending organism will be resistant to the current agent. Therefore, the culture media will not be sterilized by the excreted drugs.

Although prophylaxis effectively prevents infection, it may not reduce the recurrence rate of urinary infection after therapy has been discontinued. In one trial using TMP-SMX, all the children were treated for 2 weeks and then randomized to receive no treatment or 6 months of prophylaxis.[533] Although prophylaxis was highly effective in preventing infection, the rate of recurrent infection after stopping prophylaxis was virtually identical to that observed after 2 weeks of treatment. Similarly, Smellie et al. reported a high recurrence rate (42%) in children with a history of recurrent urinary infections following discontinuation of long-term antimicrobial prophylaxis.[534] Nevertheless, it is helpful to achieve an infection-free period in those children with a history of multiple, symptomatic urinary infections. During this period of time, aggressive efforts should be made to improve the voiding and bowel habit patterns in those children who have clinical and/or urodynamic evidence of dysfunctional voiding, a common finding in this difficult group of patients.

Antimicrobials with proven efficacy in the prevention of recurrent urinary infections include nitrofurantoin, TMP-SMX or TMP-sulfadiazine, and TMP alone.[466,534–536] In a double-blind study that compared prophylaxis with nitrofurantoin versus TMP alone in 130 children, nitrofurantoin demonstrated superior efficacy in those children with abnormal urography and/or reflux.[537] However, no differences were seen in children without urinary tract abnormalities. Nitrofurantoin did not alter the pattern of resistance of intestinal bacterial flora, while TMP significantly increased the percentage of TMP-resistant bacteria during prophylaxis. Side effects, primarily gastrointestinal, were more frequent in the nitrofurantoin group (37%) than in the TMP group (21%) ($p = 0.05$). The authors recommended nitrofurantoin as the first choice for prophylaxis in children with recurrent UTI and urinary tract abnormalities. Pure SMX is less effective, and synthetic penicillins are particularly poor prophylactic agents because of the frequent emergence of resistant organisms. Of note, these gastrointestinal side effects of nitrofurantoin can be significantly reduced by prescribing the macrocrystal formulation used in the capsular form of macrodantin. For young children who cannot swallow a capsule, these can be opened and the tasteless crystals mixed with soft food, yogurt, or ice cream.

Prophylactic doses are generally less than those used to treat acute infection. Smellie et al. effectively used 10 mg SMX plus 2 mg/kg/day TMP or 1–2 mg/kg/day nitrofurantoin in one to two doses.[534,538] Our practice is to administer one-third to one-half of the therapeutic dose once daily. Alternatively, intermittent prophylaxis with low-dose TMP-SMX every other day has also been reported to be effective in both children with VUR and preadolescent girls with recurrent infection.[538–540] In difficult cases of children who develop breakthrough UTIs on single-drug antimicrobial prophylaxis, double prophylaxis with nitrofurantoin and TMP-SMX has been shown to be effective in reducing recurrences.[541] In one study of 31 girls with recurrent breakthrough infections on single-drug therapy, 68% had VUR, 49% had voiding dysfunction, and 26% had both.[542] When treated with double-drug prophylaxis, the rate of infection was reduced from 17.4 UTIs/100 patient months to 3.6 UTIs/100 patient months ($p < 0.001$). These patients were also treated with anticholinergics and frequent timed voiding.

Earlier recommendations were based in part on the concern for long-term morbidity associated with renal scarring secondary to recurrent UTIs and VUR.

However, evidence shows that only a small subgroup of children are at risk for significant morbidity. Furthermore, not all small kidneys are the result of scarring secondary to UTI and VUR, as some are congenitally dysplastic kidneys that occur in association with high-grade VUR.[543] It has also been noted that despite more aggressive identification and treatment of VUR over the last four decades, the incidence of ESRD associated with reflux nephropathy has not decreased based on transplant registry data.[544] Consequently, the UK National Institute for Health and Care Excellence (NICE) guidelines in 2007 and the American Academy of Pediatrics (AAP) guidelines in 2011 have recommended a more selective approach to the evaluation and treatment of UTI and VUR with antibiotic prophylaxis.

Recent studies that have assessed the efficacy of long-term low-dose antibiotic prophylaxis have yielded conflicting results. A multicenter, randomized controlled noninferiority trial of children under 7 years of age with first febrile UTI were used to compare no prophylaxis with

prophylaxis for 12 months with end points of recurrent febrile UTI. Intention to treat showed no significant differences in the primary outcome between no prophylaxis and prophylaxis for febrile UTI or in a secondary outcome examining renal scarring on a 12-month DMSA scan.[545] Similar findings have been reported in other recent studies, which mostly included patients with mild to moderate VUR.[266,331,543,546] However, these trials were limited by sample sizes from 100 to 218 and therefore could not evaluate the effect of reflux severity. A subsequent meta-analysis of randomized control trials concluded that evidence is lacking that prophylactic antibiotics reduce the incidence of recurrent childhood UTI.[547] Similarly, a Cochrane review that compiled data from 20 randomized trials, including 2324 children, noted significant variation in methodologic quality, which made it difficult to form firm conclusions. However, when averaged across the studies, antibiotic prophylaxis did not appear to result in a significant reduction in febrile UTIs in children with VUR.[548]

In contrast, Craig et al. showed in the PRIVENT study that long-term low-dose TMP-SMX was associated with a decreased number of UTIs in predisposed children.[547,549] Children under the age of 18 were randomized to prophylaxis with TMP-SMX or placebo. Forty-two percent had VUR (at least grade III in 53% of these patients), and 71% were entered after their first known UTI. The investigators found a 6% absolute reduction in those receiving antibiotic prophylaxis, with 19% in the placebo group and 13% in the prophylaxis group developing a recurrent UTI. In the Swedish Reflux Trial, 203 children with grades III and IV VUR and a history of UTI were randomized to antibiotic prophylaxis, surveillance, or endoscopic treatment. Antibiotic prophylaxis resulted in a significant reduction of recurrent febrile UTIs and new renal scarring when compared with placebo. Currently, the results of the NIH RIVUR Study with 600 patients with grades I–IV VUR randomized to antibiotic prophylaxis versus placebo are awaited.

It appears to be increasingly clear that antibiotic prophylaxis is probably not beneficial in low-risk populations that are not predisposed to recurrent UTIs. In contrast, antibiotic prophylaxis does confer a therapeutic advantage in higher-risk patients, that is, those with higher grades of VUR, renal scarring, dysfunctional elimination, and/or a history of recurrent UTIs.

Inoculation with Benign Bacteria

Mutaflor® is a commensal *E. coli* strain that eradicates pathogenic bacteria from the gastrointestinal tract. It alters the intestinal biome, and theoretically, it could be used as an alternative to probiotics in the prevention of recurrent UTIs. In an experimental study, Storm et al. used in vitro assays to analyze the effectiveness of Nissle 1917 for eradicating collections of 43 bacterial pediatric uropathogens. Nissle 1917 adversely affected the growth of 34 of 43 isolates. It inhibited the growth of 21 isolates and overgrew 13 isolates, with the breakdown of 40% *Pseudomonas*; 50% *E. coli*, *Enterococcus*, and *Staphylococcus*; 100% *Klebsiella* and *Enterobacter*; and none for *Citrobacter* and *Serratia*. Since it outcompeted or inhibited most bacterial isolates in the studied library, more research is needed to determine if inoculation with Nissle 1917 could actually help prevent recurrent UTIs.[550]

APPENDIX: ANTIBACTERIAL AGENTS

Sulfonamides

Sulfonamides act by competitively blocking the conversion of para-aminobenzoic acid to folic acid.[551] About 75% of the oral dose is absorbed. Free sulfonamide is excreted into urine by filtration and tubular secretion. Although high tissue levels are not achieved, excellent urine levels result. Sulfonamides are most effective against *E. coli*, but also may be effective against other gram-negative and gram-positive organisms.

Sulfonamides are well tolerated by children, are inexpensive, and produce few side effects. They affect the gastrointestinal flora when used for long-term prophylaxis but are effective agents for short-term acute therapy of uncomplicated infections. They displace protein-bound bilirubin and hence in the neonate have the potential to interfere with bilirubin excretion and cause jaundice. Once the infant has passed through the period of "physiologic jaundice," these agents can be utilized safely. Some patients are allergic to sulfa, but fortunately, most reactions are of a minor cutaneous nature, such as urticaria. There have been some problems with major hypersensitivity reactions, such as the Stevens–Johnson syndrome, but these are rare. The most widely used agent is sulfisoxazole, employed in a dose of 120–150 mg/kg/day, given acutely in four to six divided doses orally.[552]

Trimethoprim-Sulfamethoxazole

The TMP-SMX combination is useful both in the management of simple cystitis and for long-term antibacterial prophylaxis. This combination has a diminished effect on bowel flora and offers the advantage of TMP entering vaginal secretions in the adult female.[553] This latter characteristic appears to be of particular utility in its effectiveness as a prophylactic agent. In addition, trimethoprim has also been shown in vitro to induce phase variation of fimbriated *E. coli* to a nonfimbriated state.[554] This and the high concentration in vaginal secretions work to prevent vaginal and periurethral colonization with organisms that could potentially cause UTI. TMP interferes with dihydrofolic acid reductase, and sulfa blocks the conversion of para-aminobenzoic acid to dihydrofolic acid. The combination is effective against many gram-negative as well as gram-positive organisms. It is well absorbed, attains high levels in both serum and urine, and is well tolerated by children. Neutropenia and thrombocytopenia are not uncommon with its use. However, the significance of these changes is unknown.[555]

The combination is available as a suspension containing 40 mg of TMP and 200 mg of SMX per 5 mL. The dose employed in children over 2 months of age is TMP, 6–12 mg/kg/day, and SMX, 30–60 mg/kg/day, in two divided doses.[552]

Nitrofurantoin

Nitrofurantoin is quite useful in the treatment of simple cystitis and is also a very effective agent for long-term low-dose prophylaxis. It is thought to interfere with the early stages of the bacterial Krebs cycle.[556] It is well absorbed from the gastrointestinal tract and has minimal effect on bowel flora. Hence, the resistance rate of UPEC has remained low. Tissue levels are low because it is excreted almost entirely in the urine by glomerular filtration. Urinary levels tend to be quite high. Urinary alkalization increases urine levels, whereas acidification increases tissue levels. It works well against most *E. coli* and enterococci but is not particularly effective against *Klebsiella*, *Proteus*, or *Pseudomonas*.

Nausea and vomiting are frequent troublesome side effects in children; however, these can be minimized by administering the agent immediately following a meal or by utilizing nitrofurantoin macrocrystals supplied in capsule form. For the small child, the contents of the capsule can be emptied and administered in potatoes or applesauce.

In neonates, nitrofurantoin has the potential to cause a hemolytic anemia because of glutathione instability. Consequently, it should not be used in this age group. Additionally, the drug is ineffective in patients with significant renal impairment. Other side effects are rare but do include peripheral neuropathy and pulmonary infiltrates. The usual dose in children older than 3 months of age is 5–7 mg/kg/day given orally in three to four divided doses.[552]

Penicillins

Historically, the penicillins as a class were probably the most widely used antibiotics. All act by blocking mucopeptide synthesis in the cell walls so that the bacterium is unprotected from its high internal osmotic pressure.[557] This effect occurs only in growing cells. However, use of the penicillins in the treatment of UTIs is decreasing due to the emergence of resistant strains of uropathogenic bacteria.

Penicillin G

Extremely high urine levels can be achieved with penicillin G in patients with normal renal function, and under those circumstances, this drug may be very effective against both *E. coli* and *Proteus*. Its major toxic effect is allergy manifested by rash or anaphylaxis.

Ampicillin

Ampicillin is the most widely used penicillin in the treatment of UTIs. It is not well absorbed from the gastrointestinal tract; therefore, high fecal levels do occur and diarrhea is common. High serum and urine concentrations are achievable. This agent should not be administered to patients with a known history of penicillin allergy. The usual dose is 50–100 mg/kg/day given every 6 hours. It can be administered either orally or intravenously.[552]

Amoxicillin

Amoxicillin is a derivative of ampicillin that is absorbed more readily and therefore produces less diarrhea. It is administered orally in a dose of 20–40 mg/kg/day every 6–8 hours.[552]

Carbenicillin

Carbenicillin is an agent that may be useful in the treatment of *Pseudomonas* and indole-positive *Proteus*; however, its usefulness is often diminished by the emergence of resistant strains. It is available as tablets and as a parenteral solution. When it is used parenterally for UTI in children, the usual dose is 50–200 mg/kg/day given every 4 hours; for severe infections, the dose can be increased to 400–500 mg/kg/day.[558] The oral form is not predictably effective in children.

Ticarcillin

Ticarcillin is available for parenteral therapy only. Like carbenicillin, it is active against *Pseudomonas* and indole-positive *Proteus*, which may be resistant to other drugs. It is often used with an aminoglycoside for a synergistic effect. This combination may also delay the emergence of resistant strains. Sodium overload is less likely to occur with ticarcillin than with carbenicillin. The usual dose in children for treatment of UTI is 50–100 mg/kg/day given every 4–6 hours. In life-threatening infections, the dose can be increased to 200–300 mg/kg/day.[558]

Piperacillin

Piperacillin has essentially the same antimicrobial spectrum as carbenicillin and ticarcillin, but is more effective on a weight basis. Piperacillin may have some advantage in allowing lower doses and therefore less sodium load than carbenicillin and ticarcillin. The dosage in children is 50 mg/kg/day given every 4–6 hours.[558]

Cephalosporins

Cephalosporins are usually effective against most of the gram-negative and many of the gram-positive pathogens. Excretion is by both glomerular filtration and tubular secretion. Although there can be some cross-reactivity in patients who are allergic to penicillin, in general these agents can be cautiously administered to patients with penicillin allergy.

Oral Drugs

Oral cephalexin, a first-generation cephalosporin, is well absorbed from the gastrointestinal tract and can be given in a dose of 25–50 mg/kg/day every 6 hours.[552] Cefaclor, a second-generation oral cephalosporin, is somewhat more active against gram-negative bacteria but is more expensive than cephalexin. The dosage is 20–40 mg/kg/day given every 8 hours.[552] Other oral cephalosporins include cephradine (first generation) and cefadroxil (second generation). A new third-generation cephalosporin for oral administration, cefixime, is available. In addition to

broader coverage of gram-negative organisms, an advantage of cefixime is a prolonged half-life, allowing for once or twice daily dosage. The recommended dose for children is 8 mg/kg/day in one or two divided doses.[559]

Parenteral Drugs

Numerous cephalosporins are available for parenteral use. The first-generation cephalosporins (cephalothin, cefazolin, cepharadine, and cephapirin) are useful agents for urinary infections caused by most strains of *E. coli*, *Klebsiella*, and *Proteus*, but not *Pseudomonas*. As with all cephalosporins, they are inactive against enterococci. The second-generation parenteral cephalosporins (cefamandole and cefoxitin) are more active than the first-generation agents against many enteric gram-negative bacteria, but not *Pseudomonas*. Cefoxitin is the most active cephalosporin against anaerobes, including *Bacteroides fragilis*. There are a number of new third-generation cephalosporins (cefoperazone, cefotaxime, ceftazidime, and ceftriaxone). These drugs have been developed because of their relatively greater activity against gram-negative bacteria. Although most retain some activity against gram-positive bacteria, they are much less active than first-generation cephalosporins for staphylococci or other gram-positive bacteria. Ceftriaxone has a longer half-life, allowing for once or twice daily dosage. It is also more active than cefoperazone against most gram-negative bacteria.

Other Cephalosporins

There are so many new cephalosporins that it is difficult to choose among them: cefoxitin, cefotetin, cefmetazole, and flomoxef. Cephamycins are β-lactam antibiotics that are similar to cephalosporins and are classified as second-generation cephalosporins. It is recommended that the physician become familiar with the use of one oral and one parenteral drug in each generation. Dosage in children varies with each cephalosporin.

Aminoglycosides

The aminoglycosides are well tolerated by children and are of special utility in the treatment of complicated gram-negative UTI. They interfere with protein synthesis by binding proteins of the bacterial ribosomes.

Gentamicin

Gentamicin is probably the most widely used of the aminoglycosides in children and is especially effective against *Pseudomonas*. The usual pediatric dose is 5–7.5 mg/kg/day parenterally in two divided doses, depending on age.[552] It achieves high tissue concentration and can be ototoxic, particularly to the vestibular cells. Nephrotoxicity also occurs in a small percentage of patients and should be watched for by checking serum creatinine periodically during the course of therapy. Nephrotoxicity occurs particularly frequently when gentamicin is given in combination with cephalosporins. Both ototoxicity and nephrotoxicity are usually transient.

Tobramycin

Tobramycin has the advantage of particular efficacy against *Pseudomonas*. It is said to be less nephrotoxic than gentamicin.[560] The dosage is 4–7.5 mg/kg/day given every 8–12 hours, depending on age.[552]

Amikacin

Amikacin was developed to improve activity against emerging resistant strains of *Pseudomonas*. As with other aminoglycosides, it is potentially both nephrotoxic and ototoxic. The dosage is 15–22.5 mg/kg/day given every 8 to 12 hours, depending on age.[552]

Tetracyclines

Tetracyclines should not be used in children under 8 years of age because they stain the permanent teeth. The need for tetracycline is extremely unusual in modern-day pediatrics.

Clavulanic Acid

Clavulanic acid is a β-lactam structurally related to the penicillins, but it has little antimicrobial activity alone. It inactivates a wide variety of β-lactamases by blocking the active sites of these enzymes. Clavulanic acid is particularly active against the clinically important plasmid-mediated β-lactamases frequently responsible for transferred drug resistance to penicillins and cephalosporins.[561] Clavulanic acid is commercially available in combination with amoxicillin as Augmentin. The recommended pediatric dose of Augmentin is based on patient weight less than 40 kg. For severe infections, 40 mg/kg/day is given every 12 hours. For less severe infections, 20 mg/kg/day is given every 12 hours. For neonates and infants less than 3 months of age, the recommended dosing is 30 mg/kg/day based on renal excretion. For patients weighing greater than 40 kg, it is recommended that adult dosing guidelines be followed.

Carbapenems

Carbapenems are a β-lactam antibiotic that are effective against gram-positive, gram-negative, and anaerobic bacteria with the exception of intracellular bacteria. These antibiotics readily penetrate the bacterial cell walls to inhibit cell wall synthesis. The structure of these drugs provides stability that enables them to be extremely resistant to most β-lactamases.[562] Some gram-negative bacteria with decreased porin production have decreased cell wall permeability, leading to increasing resistance. Increasing resistance patterns have been seen particularly in extended-spectrum β-lactamase (ESBL) *E. coli* that will likely have a serious impact on our ability to treat multidrug-resistant UTIs.[563] This class of medications includes imepenem, meropenem, ertapenem, and doripenem. The recommended dosing for meropenem is 20 mg/kg, up to maximum of 1 g every 8 hours. Ertapenem for children over 13 years of age is 1 g daily, but for children 3 months to 12 years, the recommended dosing is 15 mg/kg every 12 hours, not to exceed a maximum dose of 1 g daily.

Quinolones

Flouroquinolones are bactericidal agents that work by inhibiting the essential bacterial enzyme DNA gyrase, which is essential for DNA replication in bacterial cells.[564] Fluoroquinolones have been associated with arthropathy and histopathologic changes in weight-bearing joints of juvenile animals. For this reason, ciprofloxacin has been avoided in pediatric populations. Recently, the AAP has approved the use of fluoroquinolones to treat certain infections. One specific approved use of ciprofloxacin is in childen older than 1 year of age with complicated UTIs and pyelonephritis.[481] This medication is reserved for multi-drug-resistant populations of patients and/or patients in which oral ciprofloxacin enables the patients to avoid long-term intravenous therapy. For complicated UTIs for patients age 1–17, the recommended dosing is 10–20 mg/kg orally every 12 hours or 6–10 mg/kg intravenously every 8 hours. The maximum recommended doses are 400 mg/dose intravenously and 750 mg/dose orally.

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CHAPTER
8

Fungal, Parasitic, and Other Inflammatory Diseases of the Genitourinary Tract

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FUNGAL INFECTIONS OF THE URINARY TRACT

Candidiasis

Pediatric fungal UTIs have increased in prevalence with the rising number of preterm infants receiving aggressive neonatal intensive care unit (NICU) management and the increasing numbers of immunocompromised pediatric patients surviving malignancies, HIV, and solid organ and bone marrow transplantation. In preterm infants and children, predisposing risk factors may include broad-spectrum antimicrobial therapy; intravenous, urinary, or umbilical artery catheterization; long-term parenteral nutrition; low birth weight; fungal colonization; congenital conditions; and immunocompromised status. The incidence of invasive candidiasis in the NICU increases with decreasing birth weight, with rates as high as 10% reported in extremely low-birthweight (ELBW) (<1000 g) infants.[1] The spectrum of *Candida* infection ranges from catheter-associated candidemia to single-organ or disseminated infection. The urinary tract may act as a primary route of entry in the form of candiduria or as a site of disseminated infection, as in renal candidiasis manifested as renal fungal balls or renal parenchymal infiltration.

Candida species are the leading isolate associated with fungal UTIs in the pediatric population, with *Candida albicans* as the most common of these opportunistic mycoses, accounting for more than 50% of cases. *Candida parapsolosis* has become the second most common species after *C. albicans*, due to the extensive use of indwelling catheters. *C. albicans* is a yeast that belongs in the commensal flora of the mouth, intestinal tract, vagina, and skin. *Candida* is the most common opportunistic mycosis. The same clinic risk factors that predispose to candidemia also heighten the risk of candiduria. Risk factors include ELBW infants, extreme prematurity, central venous catheters, parenteral nutrition, indwelling Foley catheters, steroid administration, the use of H2-receptor antagonists, the use of broad-spectrum antibiotics, and the presence of congenital urinary tract anomalies.[2] Systemic candidiasis is found in 35%–52% of cases of neonatal candidal UTI.[3] The frequent association of candiduria and candidemia supports the role of systemic antifungal treatment.

Pediatric patients with candidal UTIs can present with a range of symptoms, from fever, lethargy, feeding intolerance, respiratory distress, and abdominal distention to frank urosepsis in cases of renal candidiasis.[4] In patients with localized *Candida* cystitis, symptoms often consist of urinary frequency, urgency, and dysuria. Common laboratory features include a leukocytosis with "left shift" and thrombocytopenia. Renal candidiasis may present with either a nonoliguric acute renal failure, with a rising serum creatinine in the face of normal urine output, or an anuric renal failure due to urinary obstruction caused by ureteral fungus balls.[5] Renal pelvis fungus balls have been found at a rate as high as 35% in infants with candiduria who underwent renal ultrasound imaging.[6]

Diagnosis of candiduria is made by urine culture. In the neonate, appropriate methods of obtaining urine cultures include sterile urethral catheterization or suprapubic aspiration. While suprapubic aspirate has generally been considered the "gold standard," it is not routinely performed in the NICU, but rather sterile urethral catheterization is considered the most efficient collection method. A suprapubic aspirate with $>10^3$ or $>10^4$ CFU/mL via urethral catheterization has been previously defined as indicative of candidal UTIs. Urine specimens taken from indwelling catheters may have colony counts as high as 10^5/mL with no relationship to upper tract candidal infection.

Renal candidal involvement may be secondary to systemic infection, during the course of candidal cystitis, or may be involved primarily without other organ involvement. Renal ultrasound imaging has been the imaging modality of choice in the diagnosis of renal candidiasis because of its portability, noninvasiveness, and lack of radiation exposure. Typical ultrasonographic features of renal candidiasis consist of an enlarged and echogenic kidney with a dilated pelvicalyceal system filled with fungus balls (Figures 8.1 and 8.2).[7] Fungus balls are commonly described as a nonshadowing echogenic focus.[8] While this finding is nonspecific, and may represent blood clot, fibrinous deposits, or nephrocalcinosis, it is highly suggestive of renal candidiasis, when taken within the clinical context of a positive blood or urine culture for *Candida* species. Currently, there is limited experience with computed tomography (CT) and MRI of renal candidiasis. The CT appearance of fungus balls

FIGURE 8.1 Candidal fungus balls in a 4-week-old boy. (From Mercado-Deane M. et al. *Radiographics* 2002;22:1429–38.)

is that of collecting system soft tissue masses without mass effect (Figure 8.3).[9] MRI has been reported to be superior to CT delineation of renal candidiasis, with T2-weighted and short tau inversion recovery (STIR) sequences the best for distinguishing between fungal infiltrates and urine. However, ultimately the greater portability and the ease of sequential imaging have made ultrasound the imaging method of choice to date. At present, renal ultrasound imaging is recommended in the setting of a positive urine culture for *Candida*, persistent candidemia, or cases of systemic candidiasis associated with a rising serum creatinine. Some authors have recommended serial ultrasound imaging, as a normal renal ultrasound at the onset of candiduria cannot exclude the later development of renal involvement. In a study by Bryant et al., more than half of candiduric infants were

FIGURE 8.2 Candidal bezoar and renal dilation. (From Mercado-Deane M et al. *Radiographics* 2002;22:1429–38.)

FIGURE 8.3 Abdominal CT shows multiple low-density lesions in both kidneys consistent with primary renal candidiasis. (From Li W.-Y et al. *Kidney Int* 2007;72:382.)

found to have renal infiltration as late as 8–39 days after an initially normal imaging study.[3]

The treatment of candiduria is dependent on the extent of infection. Candiduria that occurs in otherwise healthy children after long-term broad-spectrum antibiotics should clear spontaneously after the antibiotics are stopped. A wide range of therapies have been reported, including urinary tract irrigation with antifungal agents, systemic antifungal therapy, nephrostomy decompression, nephrectomy, and drainage of perinephric abscesses. Surgical management has been reserved for cases of urinary obstruction and renal abscess formation, with the vast majority of cases effectively managed medically. Symptomatic infections limited to the lower urinary tract may be eradicated by bladder instillations and irrigations with a solution of amphotericin B (5–15 mg in 100 mL of sterile water, allowed to dwell for 60–120 minutes, three or four times daily).[10] Upper tract candidal infection may be treated with nephrostomy tube irrigation with amphotericin solution or oral 5-flucytosine. It should be noted, however, that 5-flucytosine should be avoided in children with azotemia or bone marrow suppression. The American Academy of Pediatrics Committee on Infectious Diseases has recommended amphotericin B as the drug of choice for systemic candidiasis, without any mention of candiduria treatment guidelines.[9] Treatment of candiduria with nonobstructive renal candidiasis has thus been extrapolated from these recommendations. Current treatment protocols consist of amphotericin B at 1 mg/kg/day, with or without 5-flucytosine, for 7–14 days after blood and/or urine cultures become negative. Unfortunately, no randomized trials have been performed outlining the appropriate duration of antifungal therapy. The persistence of renal ultrasound abnormalities despite prolonged systemic antifungals and sterile urine cultures makes recommendations for treatment duration even more problematic. Amphotericin B is nephrotoxic and must be meticulously titrated to obtain appropriate serum levels, and monitoring of serum creatinine is necessary, with prolongation of the dosing interval in the event of

a rising serum creatinine. Additional toxic side effects include fever, nausea, vomiting, malaise, and renal failure. Liposomal formulations are not recommended due to their poor renal penetration.

Other antifungal agents include fluconazole, caspofungin, micafungin, and anidulafungin. Unfortunately, clinical data on these other antifungals are limited in the neonate and pediatric population. Fluconazole, which has been associated with less nephrotoxicity than amphotericin B, is used with caution due to its lower efficacy against non–*C. albicans* species.

Obstructive uropathy caused by renal candidiasis is typically treated surgically. Obstructing fungus balls have been removed by pyelotomy, percutaneous abscess drainage, insertion of nephrostomy tubes with direct amphotericin irrigation, or even nephrectomy in severe cases. Rapid diagnosis and systemic antifungal therapy have become the standard of care, making the need for surgical intervention quite rare. However, whenever obstructive nephropathy is present, a pediatric urologist should be promptly consulted to evaluate the necessity of surgical intercession.

Aspergillosis

Aspergillosis refers to the spectrum of diseases caused by the mycelial fungi of the genus *Aspergillus*. Currently, *Aspergillus fumigatus* and *Aspergillus niger* are the most common strains. Aspergillosis is the second most common opportunistic fungal infection in the immunocompromised pediatric patient population.[11] *Aspergillus* is a widely disseminated saprophyte in soil, and has been isolated from moist environments, such as air-conditioning systems.[12] Outbreaks of invasive disease usually occur among immunocompromised children as a result of exposure to aerosolized spores. Inhalation of the airborne spores allows entry of the pathogen into the body, at which point in the setting of immunocompromise, the organism is widely disseminated through hematogenous spread. Other potential portals of entry include open operative wounds or indwelling foreign bodies, such as intravenous or urinary catheters. Invasive forms of aspergillosis have increased as a reflection of the improved survival of immunocompromised children and advances in the treatment of children with organ transplantation and hematopoetic stem cell transplant (HSCT). The single greatest risk factor for invasive *Aspergillus* in these settings is neutropenia.

Invasive aspergillosis has been fairly well characterized in the literature, but very few studies describe the clinical features, diagnosis, and ideal treatment for pediatric genitourinary involvement. Rare case reports document cases of *Aspergillus* fungus balls in the setting of bladder exstrophy and HSCT.[12] Microscopic hematuria and pyuria are commonly present in patients with aspergillosis. The fungi may be identified as branched septate hyphae on potassium hydroxide preparations of infected urine. Results of urine culture are often inconclusive, and multiple cultures may be necessary to make a diagnosis. Recent advances in invasive aspergillosis diagnostics include the galactomannan (GM) assay, a major cell wall constituent that can be assayed in serum; a beta-D glucan serum assay; and *Aspergillus* polymerase chain reaction (PCR) testing. Unfortunately, there are limited data as of yet in the pediatric population for these serological diagnostic tests. As with candidal urinary involvement, renal ultrasonography remains the most effective method for the detection of fungus balls.[13]

FIGURE 8.4 Renal aspergillosis in the setting of Acute Lymphoblastic Leukemia (ALL). Notable findings include poorly enhancing, low-attenuation, mass-like renal parenchymal lesion extending to the renal sinus. Aspergillosis may also cause vascular occlusion and multiple renal infarcts. The parenchymal lesions may be difficult to radiographically distinguish from primary renal tumors. (From Rha SE et al. *Radiographics* 2004;24:S117–31.)

Obstructive uropathy resulting from an aspergilloma in the renal pelvis or the bladder is a matter of rare case reports. Renal aspergillosis is typically characterized by focal microabscess formation, hyperechogenic material in the renal pelvis, and occasionally papillary necrosis (Figure 8.4).[14]

Treatment of invasive aspergillosis with renal involvement remains a combination of systemic antifungal agents, placement of percutaneous nephrostomy catheters, and local irrigation.[16] High-dose amphotericin B and voriconazole remain the leading options in systemic antifungal treatment. Currently, voriconazole, due to its decreased risk of nephrotoxicity, is considered the superior agent. Finally, percutaneous or open surgical removal of large obstructing aspergillomas may sometimes be necessary.[15]

Coccidioidomycosis

Coccidioidomycosis is a fungal infection caused by the dimorphic fungus *Coccidioides immitis*, found principally in the soil of the southwestern United States. Endemic areas in the United States include southern California, Arizona, Texas, and New Mexico. Mexico and South and Central America are additional endemic regions. Human

infection is acquired by inhalation of airborne fungal spores. Most patients have a mild, self-limited illness characterized by upper respiratory tract symptoms; however, disseminated disease with more severe extrapulmonary symptoms is more common in immunocompromised patients (HIV, cancer, and transplant patients), infants, and non-Caucasian individuals.[17]

Disseminated coccidioidomycosis is typically characterized by infection of the skin, bones of the hand, feet, skull, and spine, as well as meningeal involvement. Genitourinary involvement is thought to occur through the hematogenous route. An autopsy series of 214 patients with disseminated disease described renal infection in 27%, prostatic infection in 2%, and epididymal involvement in 1%.[18] Immunosuppressive chemotherapy, lymphopenia, HIV, and organ transplantation have been described as some of the most important risk factors for disseminated disease. Maternal–fetal transmission, either transplacentally or perinatally, is rare, with only a handful of case reports in the literature.[19] Unfortunately, infants who acquire the disease in the postnatal period are reported to have a much higher mortality rate than older children and adults.

Genitourinary symptomatic presentation may occur simultaneously with pulmonary involvement, or may present more indolently, if at all. Often, diagnosis is delayed due to nonspecific or more latent presentations. Microscopic hematuria, pyuria, scrotal swelling, epididymal induration, and tenderness may be present in those with urinary and epididymal involvement. Coccidioidal infection of the kidney is typically confined to the cortex as small miliary granulomas or microabscesses. Large obstructive lesions within the renal pelvis do not occur as with other fungal infections.

The primary difficulty in the diagnosis of coccidioidomycosis infection is failure to consider the disease. Culture and serologic testing remain the gold standard for identification of infection. Tissue specimens may demonstrate coccidioidal spherules (Figure 8.5), which are pathognomonic for the disease, and the presence of surrounding granulomatous inflammation. Urine culture is very useful for establishing genital tract infection with *C. immitis*, as the fungus grows well on most culture medium.[20] Serologic testing with the mycelial phase antigen, coccidioidin, is a very reliable means of antibody testing. The radiographic findings of advanced renal coccidioidomycosis are generally similar to those of renal tuberculosis, characterized by infundibular stenosis, blunted or sloughed calyces, and calcified granulomas.

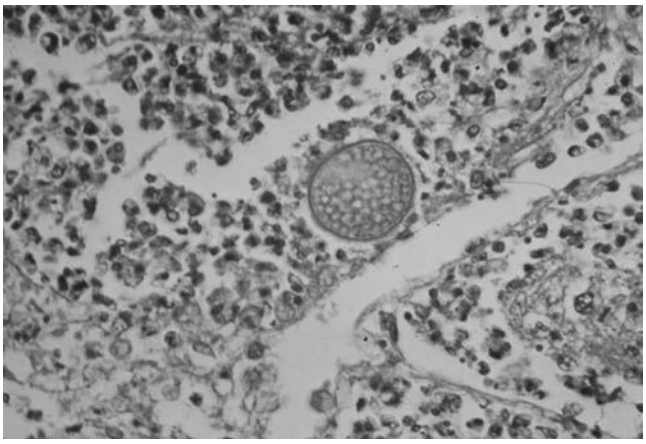

FIGURE 8.5 Mature spherule containing endospores of *C. immitis*. (Courtesy of http://phil.cdc.gov/phil_images/20030610/12/PHIL_480_lores.jpg.)

Treatment with prolonged antifungal chemotherapy is indicated for those at high risk for severe coccidioidomycosis and those with recognized disseminated infection. Amphotericin B is again the gold standard agent in pediatric patients with rapidly progressive disease. Oral azoles, such as fluconazole and ketoconazole, are alternative options. The management of isolated genital tract involvement has not been well defined in the literature. The overall treatment duration depends on the resolution of symptoms and signs, as well as the serologic response, with most practitioners administering antifungal therapy for a total of 2–3 months.

PARASITIC INFECTIONS OF THE URINARY TRACT

Schistosomiasis

Schistosomiasis is a tropical parasitic disease that infects nearly 200–300 million individuals globally, with the highest prevalence and intensity of infection primarily in children and adolescents. The two most common species are *Schistosoma haematobium* and *Schistosoma mansoni*. Urinary schistosomiasis, or bilharziasis, is a vascular parasitic infection caused by the blood fluke *S. haematobium*. The disease is endemic in Egypt and has spread to areas of Africa, Asia, South America, and the Caribbean. Prevalence is increasing in many areas, as population density increases and new irrigation projects provide broader habitats for vector snails. Imported cases into Europe have risen with the expansion of international travel. Rare cases are seen in the United States and almost always originate from an endemic area.

Humans are infected through contact with water contaminated with cercariae, the free-living infective stage of the parasite. These organisms emerge from infected snails and penetrate the intact human skin. The cercariae develop into schistosomula in the subcutaneous tissues and then migrate to the portal circulation, where they reach sexual maturity. The adult worms then migrate to the perivesical and periureteral venous plexus. Upon fertilization, female worms deposit eggs in the small venules, which eventually reach the lumen of the urinary tract. Eggs are passed into freshwater, where they hatch, infect freshwater snails, and begin the cycle anew (Figure 8.6). The entire life cycle ranges from 6 to 10 weeks in duration.

Humans become infected with *Schistosoma* after coming in contact with contaminated water. Children are most at risk due to activities such as swimming, bathing, and drinking contaminated water sources. Acute schistosomiasis occurs between 3 and 9 weeks after infection and coincides with deposition of eggs in the bladder wall.

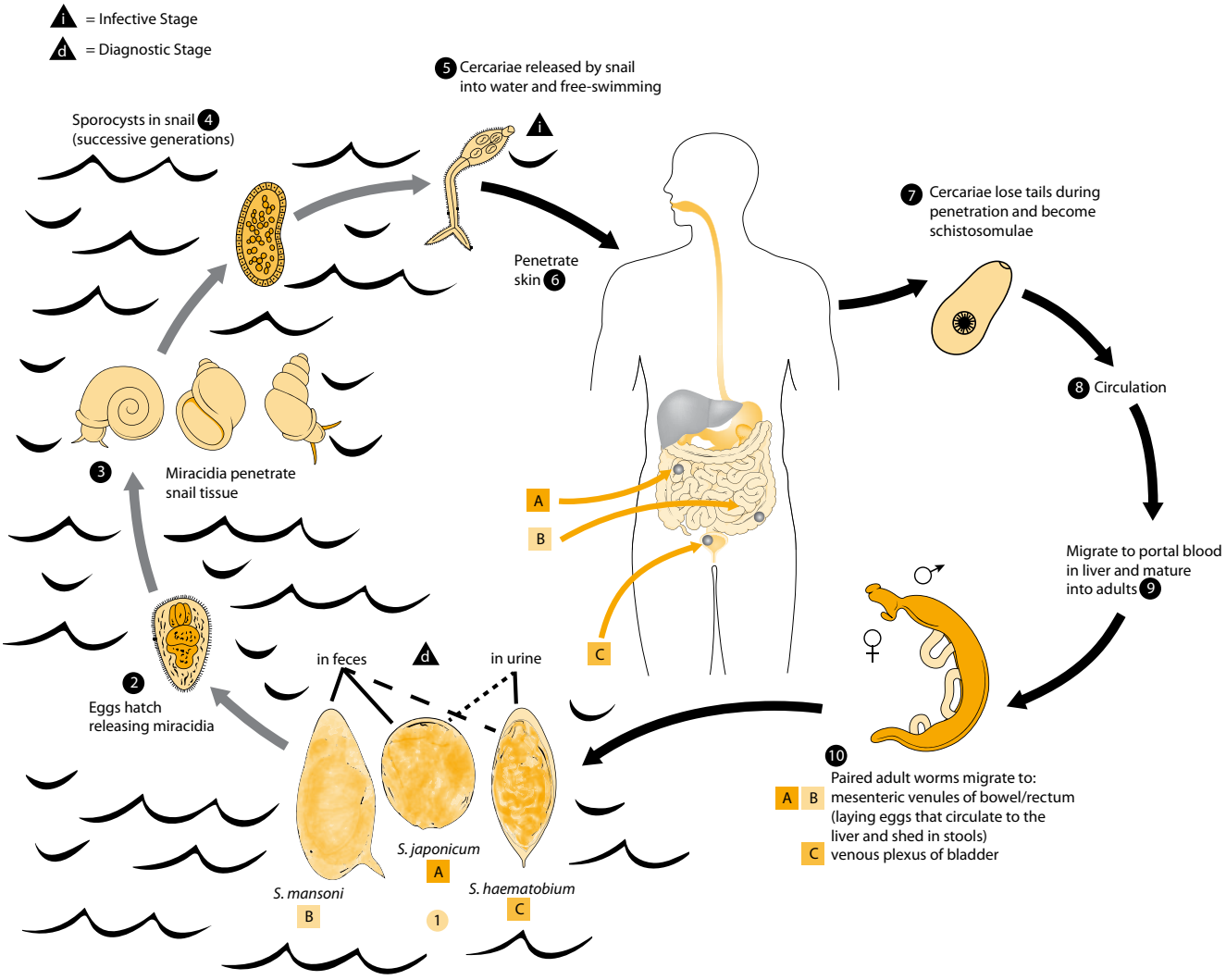

FIGURE 8.6 Life cycle of schistosomiasis parasite. (From the Centers for Disease Control and Prevention, U.S. federal government public domain archive image.)

The pathogenesis of schistosomiasis is due to the reactions to toxic, antigenic, and excretory products of the various developmental stages of the parasite.[21] The classic symptoms and signs are terminal hematuria, dysuria, leukocyturia, and nocturia. Hematuria can be so severe as to result in anemia. Severely infected patients may go on to develop obstructive uropathy with resultant renal failure. Chronic infection may lead to the most serious pathological consequences, namely, fibrosis, bladder contracture, and ureteral strictures. The disease process is insidious, and gross hydroureteronephrosis with renal insufficiency may occur before clinical symptoms appear. Persistent gross hematuria has been reportedly the most consistent clinical finding in endemic regions.

Vester et al. documented the prevalence of schistosomiasis infection in an endemic region of Mali by screening 824 villagers.[22] Infection ranged from 77% in adolescents to 51% in adults older than 40 years of age. Intensity of infection was generally low, with 91% excreting less than 100 ova per 10 mL of urine. Bladder wall thickening and irregularities, bladder masses, and dilation of the upper tracts were found ultrasonographically in approximately one-third of individuals. Bladder lesions were more frequent in children than adults and correlated well with the intensity of the infection in younger age groups.

Schistosoma eggs produce a marked eosinophilic infiltrate within the bladder wall. As the disease progresses, collagen infiltration and progressive bladder fibrosis occur. There is deposition of calcareous material and ultimately sclerosis of the bladder due to gradual calcification. Mucosal hyperplasia, squamous metaplasia, and epithelial dysplasia of the urothelium may occur at any stage of the disease process. Involvement of the trigone and bladder neck is most pronounced. Eventual bladder neck fibrosis may lead to outlet obstruction. Resultant urinary stasis and urinary infections can lead to the formation of bladder calculi, whereas chronic bladder irritation predisposes these patients to squamous cell carcinoma. Vesicoureteral reflux is commonly reported in up to 50% of these patients as a result of fibrosis and lateral displacement of the intramural ureter.

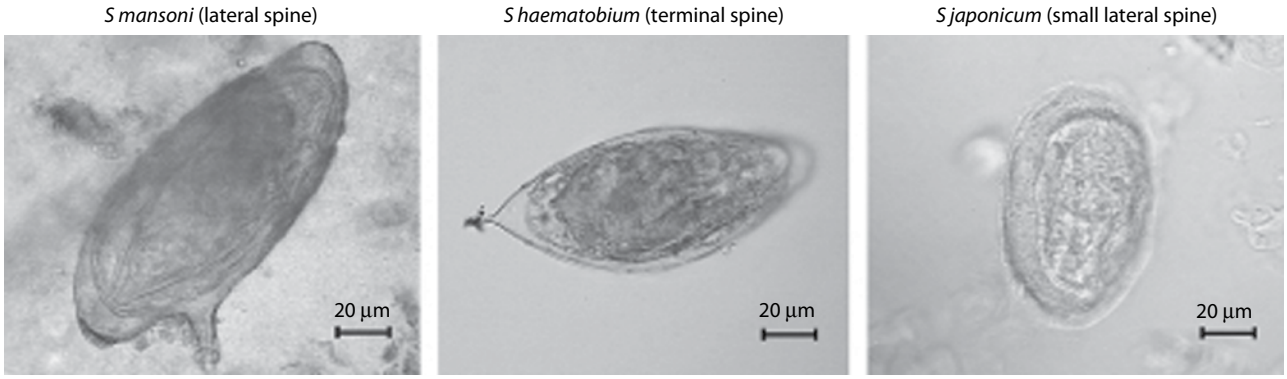

FIGURE 8.7 Microscopy of the various eggs of the *Schistosoma* species. (Courtesy of Gryseels B. *Lancet* 2006;368:1106–18.)

The gold standard for the diagnosis of schistosomiasis is established by the presence of terminal-spined eggs seen on microscopic examination of urine (Figure 8.7).[23] A 24-hour urine collection with microscopic examination of the urine concentrated by sedimentation, centrifugation, or filtration is typically recommended. The intensity of infection is expressed in terms of number of eggs per 10 mL of urine. Peripheral blood examination will usually show eosinophilia. Anemia may be present with chronic infection due to destruction of erythrocytes by the blood fluke.[24] Antibody-based assays by enzyme-linked immunosorbent assay (ELISA), indirect hemagglutination, or immunofluorescence are very sensitive; however, they cannot distinguish between a history of *Schistosoma* exposure and acute infection.[23] Cystoscopy and bladder biopsy may be performed in cases of negative urinalysis, as well as to further characterize bladder involvement.

Abdominal plain film, as well as ultrasonography, allows visualization of bladder, ureteral, and renal involvement. Calcification of the bladder wall, described as an "eggshell appearance" on plain film, is classic for chronic urinary schistosomiasis (Figures 8.8 and 8.9).[25] Hydronephrosis secondary to ureteral stricture may be found on imaging studies of the urinary tract. On cystoscopic evaluation of the bladder, bilharzial tubercles predominate over the trigone and posterior bladder wall. In patients with chronic disease, fibrosis and calcification of these parasitic nodules in the submucosa form dull, granular "sandy patches" that resemble grains of sand under water. Chronic schistosomiasis has been implicated in the later development of squamous cell carcinoma of the bladder (Figure 8.10).

Management of children with schistosomiasis should be based on an appreciation of the intensity of the infection and the extent of the disease. There are several drugs available for the treatment of urinary schistosomiasis. Most carry with them significant side effects. Praziquantel is currently the drug of choice. It is effective against all species of *Schistosoma*. The recommended regimen is to administer the drug orally as a single or divided dose of 40–60 mg/kg body weight.[26] The side effects of the drug are often quite mild, notably nausea, emesis, malaise, and abdominal pain. After a single dose, 70%–100% cease to excrete the parasitic ova. At times, a single repeat dose 6–12 weeks later is recommended to treat prepatent infections.

Surgical intervention in schistosomiasis should be reserved until the effects of medical management are

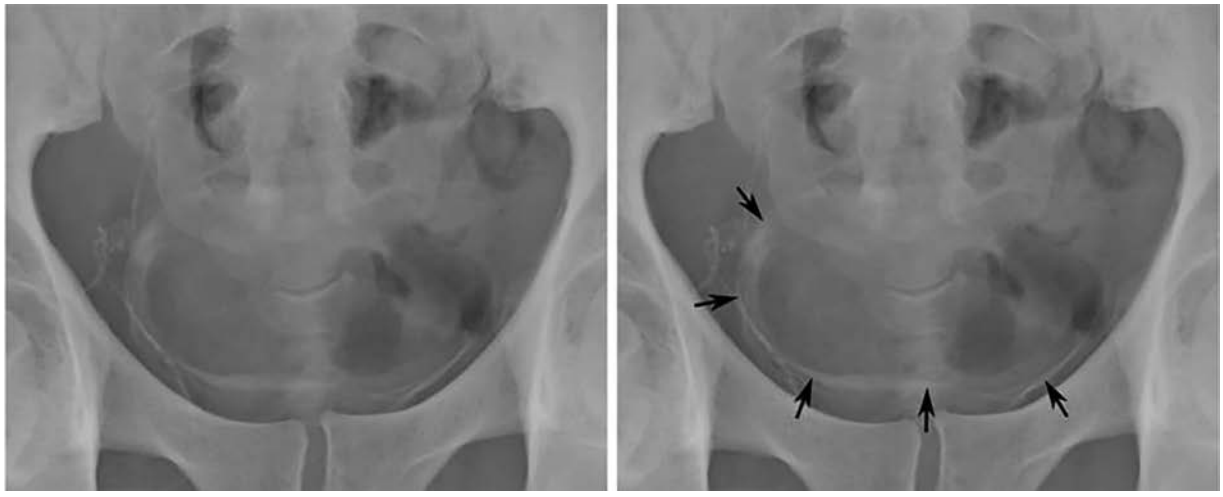

FIGURE 8.8 Plain abdominal film of urinary schistosomiasis. Note the classic eggshell calcification of the bladder wall. (From WikiMedia Commons, online repository of freely licensed media.)

FIGURE 8.9 Bladder schistosomiasis. Axial CT scan demonstrating circumferential bladder wall calcification extending to the left ureter. (Courtesy of Wong-You-Cheong JJ et al. *Radiographics* 2006;26:1847–68.)

assessed. Fibrosis and contracture of the bladder may require autoaugmentation, intestinal augmentation, or bladder replacement. Bilharzial strictures of the lower ureter can produce obstructive uropathy. Unfortunately, the extensive fibrosis of the ureteral wall and the bladder mucosa usually precludes traditional ureteroneocystostomy by submucosal tunneling. Bazeed et al. suggest a method of partial flap ureteroneocystostomy to alleviate the obstruction.[27] They report it to be effective in improving or stabilizing the upper tracts in 83% of individuals. Vesicoureteral reflux may develop in as many as 30% of these individuals after surgery.

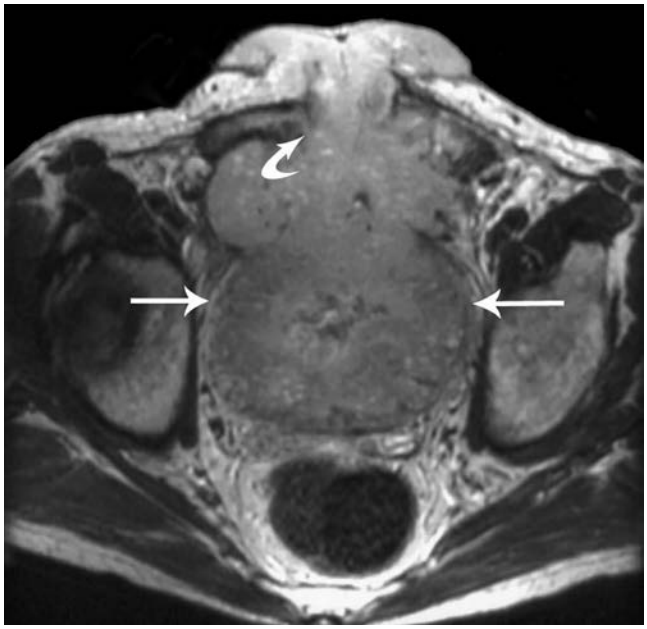

FIGURE 8.10 Invasive squamous cell carcinoma. Axial T2-weighted magnetic resonance image shows a soft tissue mass (straight arrows) filling the pelvis and obliterating the normal bladder lumen. The mass is locally aggressive and has eroded through the abdominal wall (curved arrow). (Courtesy of Wong-You-Cheong JJ et al. *Radiographics* 2006;26:553–80.)

Echinococcosis

Echinococcosis, or hydatid cyst disease, is the most prevalent human cestode infection in the world. There is virtually no part of the human anatomy that is immune from hydatid cyst disease. It is caused by the dog tapeworm *Echinococcus granulosus*. Although uncommon in the United States, it is endemic in the sheep-raising areas of the world, such as Argentina, Australia, Spain, and Greece.

Humans are an intermediate host for the larval eggs of the adult tapeworm. The adult tapeworm lives in the intestinal tracts of dogs and sheds larval eggs, which are excreted in the dog feces. Humans, as well as sheep, cattle, and pigs, may accidentally ingest these larval eggs through orofecal contamination. Dogs initially acquire the disease by swallowing the parasitic scolices in their food, which have become contaminated with the encysted parasite in the liver and lungs of sheep. This completes the life cycle of the parasite.

In humans, the larval eggs pass through the intestinal wall and are widely disseminated throughout the body. Dissemination may occur by direct, vascular, or lymphatic invasion.[28] The primary organ affected in humans is the liver. Genitourinary involvement has been documented in the kidney, ureter, bladder, prostate, and epididymis.[29] The most common location for genitourinary hydatid cyst disease in humans is the kidney. It is estimated that approximately 3% of all echinococcal infections involve the kidney.[30]

The largest series of pediatric echinococcosis was reported by Auldist and Myers, who documented 114 cases of hydatid cyst disease.[31] Children of all ages were infected; however, manifestations of the disease were infrequently evident in children under 5 years of age. This is probably a result of the slow growth pattern of the hydatid cyst. The growth rate of hydatid cysts is estimated at 1 cm/year.[32] The cyst is typically very large at the time of initial presentation. The most common site of genitourinary infestation in the pediatric population is also the kidney. Hydatid cysts of the kidney usually present as a painful flank mass. Microscopic hematuria is present in the majority of the cases. Acute flank pain may be caused by rupture of the hydatid cyst into the collecting system. The passage of scolices (daughter cysts) may be associated with gross hematuria and urinary obstruction.[33]

Ultrasonography has proved to be the most valuable tool in the diagnosis of hydatid disease. Hydatid cysts are easily demonstrated on ultrasonographic evaluation of the abdomen in children. The coexistence of hydatid disease in other organs often assists in the diagnosis. Plain films or CT of the abdomen and pelvis may also reveal calcification within the walls of these cysts (Figure 8.11a–f).[34]

As humans are infected with only an intermediate stage of *Echinococcus*, the actual parasite cannot be

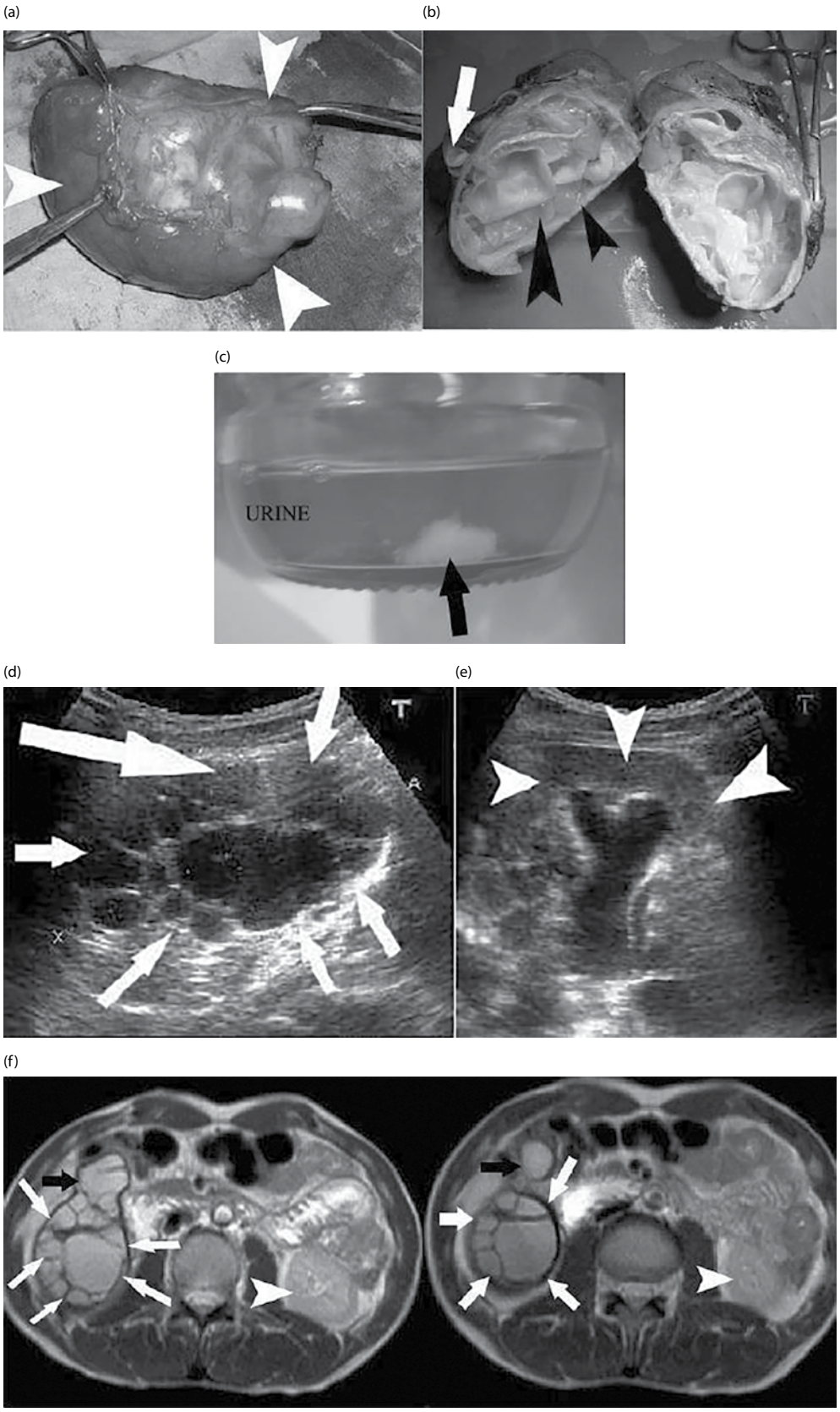

FIGURE 8.11 Renal echinococcus. (a) Postoperative nephrectomy gross specimen. (b) Cut section of kidney with hydatid cysts. (c) Urine specimen revealing hydatiduria. (d) Kidney replaced by multiseptated hydatid cysts, as seen on renal ultrasound. (e) Upper-pole hydronephrosis, as seen on renal ultrasound. (f) T2-weighted MRI demonstrating hyperintense signal from hydatid cystic disease with hypointense septae. (Courtesy of Amin U et al. *J Radiol Case Rep* 2009;3:6–11.)

routinely recovered from any easily accessible body fluid. If the hydatid cyst has ruptured into the collecting system, the recovery of scolices from the urine is pathognomonic for genitourinary echinococcosis. Serologic studies can also be useful in confirming the diagnosis of echinococcosis. Eosinophilia is reportedly present in approximate one-third of the children affected with echinococcosis. Indirect hemagglutination and ELISA testing are the most sensitive immunologic methods to diagnose human hydatidosis; however, false-positive reactions with other parasitic infections are possible.[28] Immunoelectrophoresis to detect specific antibodies against antigens isolated from hydatid cyst fluid is currently the most specific method of diagnosis of echinococcosis.[35]

Albendazole is the preferred drug for medical management of cystic hydatidosis. This drug therapy (15 mg/kg/day divided in three doses for 28 days) may be repeated for as many as four courses with 15-day drug-free intervals. A positive response may be seen in 40%–60% of pediatric patients treated.[32] Ultrasonographic indications of successful therapy include flattening of the cyst, increase in echogenicity, and detachment of membranes from the cyst capsule. The factors predictive of success with chemotherapy are age of the cyst (>2 years old), low internal complexity of the cyst, and small size.[36]

Although previously thought to be contraindicated because of the risk of anaphylaxis, percutaneous drainage of cysts under ultrasound guidance during albendazole therapy has become increasingly more successful for complete resolution of cystic disease. Spillage of cyst fluid is uncommon during aspiration. Nevertheless, systemic anaphylactic reactions are always possible with spillage of cyst fluid.

Surgical therapy is also an option for solitary lesions or failed medical management. Considerable care must be taken at the time of surgical resection to ensure that there is no rupture of the cyst or spillage of cyst fluid during removal, as viable protoscolices may contaminate the surgical field, each capable of forming a secondary cyst wherever it lodges. There is also a risk of developing anaphylaxis as a result of spillage of cyst fluid at the time of surgical resection.

Enterobiasis

Pinworm infestation (enterobiasis) is the most common helminth infection in the United States, as well as Western Europe. It is caused by the nematode *Enterobius vermicularis*. Humans are the only host, and are infected by direct anus-to-mouth transfer of eggs, which are usually carried on fingernails, clothing, or bedding. The larvae hatch in the duodenum, and the adult worm ultimately attaches to the mucosa of the large intestine, namely, the cecum, appendix, and nearby bowel (Figure 8.12). The gravid adult female worm ultimately migrates at night to the rectum and deposits her eggs in the perianal and perineal skin. Perianal irritation during egg deposition by female worms induces scratching. Eggs carried underneath the fingernails promote reinfection and autodissemination, and transfer of the disease to others. Often, the eggs are deposited in adjacent orifices as well, most commonly in the female genitourinary tract, causing recurrent UTIs and vulvovaginitis. Pinworm infection is very common among school-aged children. The peak age of infection is between 5 and 14 years of age. The estimated U.S. prevalence has been reported to be as high as 42 million cases.[37]

Enterobiasis has been implicated as a factor in acute and chronic UTIs. In a study of female children, Kropp et al. demonstrated that 22% of girls with documented UTIs had pinworm infestations compared with only 5% of an age-matched control population.[38] In a study by Ok et al., they estimated the prevalence of *Enterobius* in school-aged children with concurrent UTIs to be approximately 36%, compared with 16% in their control group.[39] They also report that the recovery of pinworms from the perianal region is higher in girls with enteric organisms present on a swab of their introitus.

The most common presentation of enterobiasis is perineal or perianal pruritis, often worse at night. Other associated symptoms commonly found are abdominal pain, anorexia, insomnia, dysuria, enuresis, vaginal discharge, and vulvovaginitis. Rarely, ectopic infections may result in endometritis, salpingitis, urethritis, epididymitis, pyelitis, pelvic inflammatory disease, or enterocutaneous fistulas. However, approximately one-third of infested children are entirely asymptomatic.

The diagnosis is typically made based on clinical history. However, definitive diagnosis is established by either finding the parasitic eggs or recovering the worms. The eggs can be easily detected by pressing adhesive tape against the perianal region early in the morning prior to bathing or defecation. The tape is then applied to a glass slide and it is examined under low-power magnification (Figure 8.13). Often, repeated examinations, usually totaling three, are necessary to make a negative diagnosis. On occasion, the threadlike yellow-white adult worms may be spotted in the stool or on toilet paper. Laboratory evaluation is typically normal, with a rare eosinophilia detected in cases of invasive disease.

Drug therapy should be given to all infected individuals. Mebendazole (100 mg single oral dose), with a repeat dose at 2 weeks, is the drug of choice. However, while its efficacy for gastrointestinal infection is cited to be around 96%, its poor absorption renders it less effective for genitourinary infections.[40] Alternative agents include ivermectin, piperazine citrate, pyrvinium pamoate, and albendazole. Kropp et al. report a greater than 50% success rate in eradicating multiple recurrent UTIs in girls with concomitant pinworm infestation when the infestation is definitively treated.[38] Unfortunately, reinfection is quite common, and adequate management typically requires the entire household to be treated simultaneously.

OTHER INFLAMMATORY DISEASES OF THE URINARY TRACT

Chlamydial Infections

Chlamydial infections in children include a spectrum of disease: perinatally transmitted infections comprising neonatal conjunctivitis, infantile pneumonia, respiratory or genital tract infections in older children, and sexually transmitted diseases in adolescents.[41] *Chlamydia*

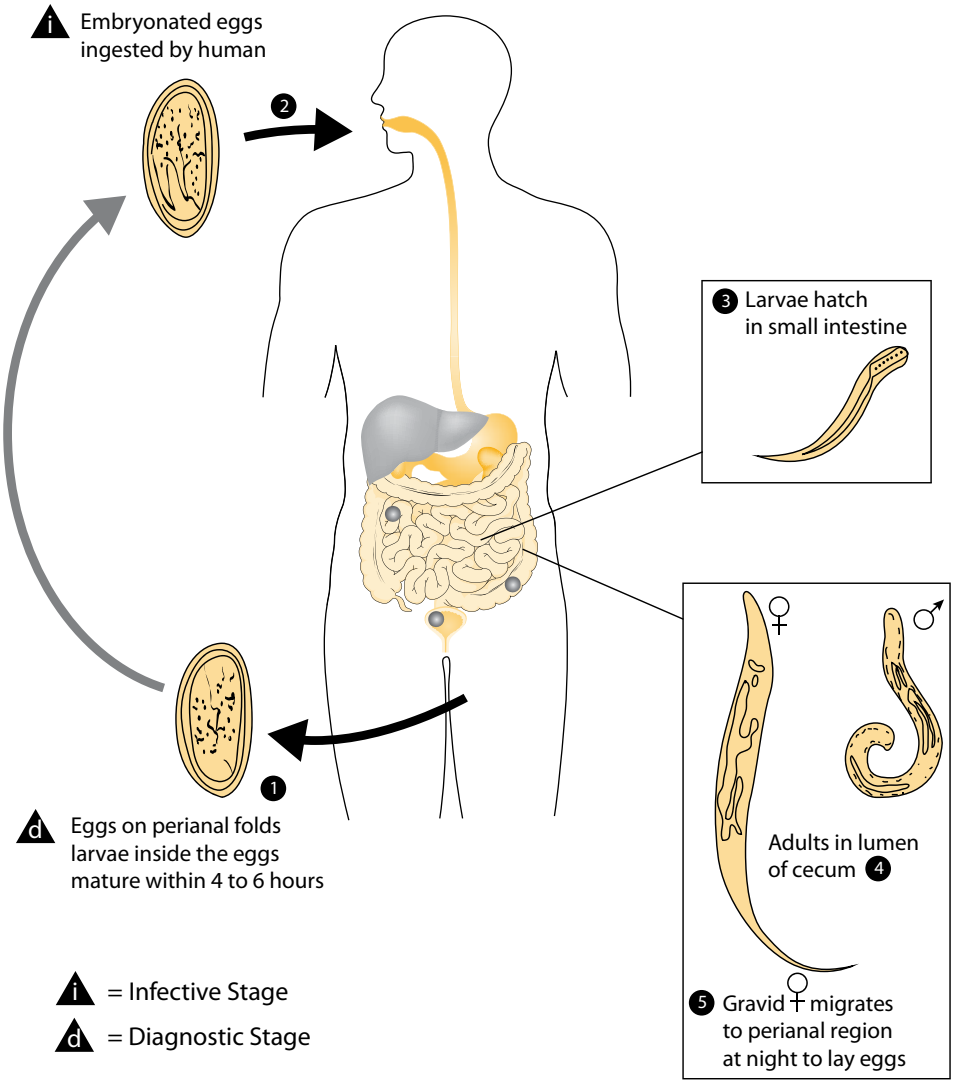

FIGURE 8.12 Life cycle of *E. vermicularis*. (Courtesy of the Centers for Disease Control and Prevention, http://www.dpd.cdc.gov/dpdx/images/ParasiteImages/A-F/Enterobiasis/Enterobius_LifeCycle.gif.)

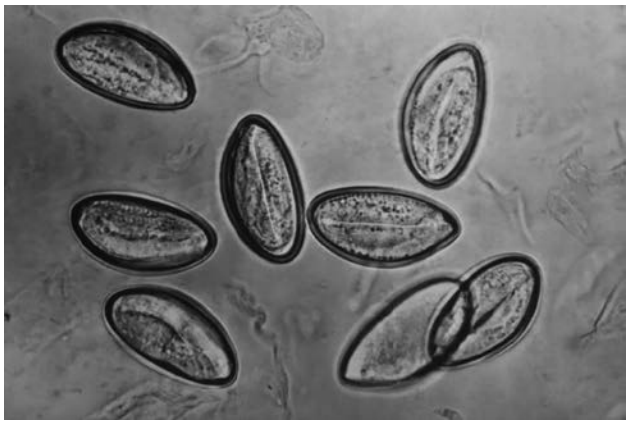

FIGURE 8.13 Enterobiasis. Demonstration of the round worm captured on cellulose tape and viewed under microscopy. (Courtesy of the Centers for Disease Control and Prevention, http://www.cdc.gov/parasites/pinworm/).

trachomatis is the only one of the four chlamydial species that commonly infects the human genitourinary tract and causes human oculogenital diseases. *C. trachomatis* is thought to be responsible for the majority of nongonococcal urethritis and pelvic inflammatory diseases in adolescents.

Chlamydia are obligate intracellular bacteria that are distinguished by a unique developmental cycle. Although they possess their own DNA and RNA, contain ribosomes, and have a cell wall, they lack the ability to generate adenosine triphosphate (ATP) and are therefore considered an energy parasite. *Chlamydia* alternate between an infectious, metabolically inactive extracellular form, the elementary body (EB), and a noninfectious, metabolically active form, the reticulate body (RB). It is the EB that binds to specific receptor proteins on the cell membrane and enters the cell by endocytosis. Within 12 hours of ingestion, the EB then differentiates into the RB form and undergoes binary fission. This results in the

typical intracytoplasmic inclusion bodies pathognomonic of a chlamydial infection. After approximately 36 hours, the RB differentiates back into an EB and is then released from the cell by a process of exocytosis.

Cervical chlamydial infections are reported in approximately 5%–30% of pregnant women. Active chlamydial infections at the time of pregnancy may be transmitted to the infant at the time of vaginal delivery. Genitourinary sites of perinatal transmission include the vagina and urethra. The risk of vertical transmission from mother to child is about 50%.[42] Neonatal conjunctivitis develops in 20%–50% of infected deliveries, while infantile pneumonia occurs in 5%–20%. Perinatally transmitted infections of the vagina, urethra, or rectum may become sites of colonization that persist for several years with minimal or no symptoms at all; therefore, the presence of *Chlamydia* is not necessarily an indication of child abuse. Currently, prenatal screening and treatment of pregnant women is the most effective strategy for preventing neonatal chlamydial infection.

The most common chlamydial infections in older infants and children include urethritis, vaginitis, and cervicitis in girls and nongonococcal urethritis and epididymitis in boys. In boys, the most common symptom of chlamydial urethritis is a clear mucoid urethral discharge. It may be associated with urinary urgency, frequency, dysuria, and scrotal pain and tenderness. In girls, acute inflammatory changes in the vagina or cervix may lead to mucopurulent discharge. Unfortunately, chlamydia is often a silent disease, only to later manifest with the long-term consequences of pelvic inflammatory disease, such as chronic pelvic pain, ectopic pregnancy, or infertility.

The definitive diagnosis of chlamydial infection includes isolation by culture of the organism from the urethra in boys and endocervical region in girls. Several nonculture methods have also been approved by the U.S. Food and Drug Administration (FDA) and include a direct fluorescent antibody test or an enzyme immunoassay. A midstream or first void urine sample is effective at capturing the chlamydial organism for the nucleic acid amplification test (NAAT). In fact, NAATs for the detection of *C. trachomatis* and *Neisseria gonorrhoeae* have largely replaced culture in many laboratories. However, none of the currently available NAATs have FDA approval for use in conjunctival or nasopharyngeal specimens from infants. Because of its high specificity and sensitivity, direct cell culture is the only test that should be used to establish the presence or absence of infections in cases with legal implications, such as pediatric sexual abuse.

Antibiotics are the mainstay of therapy for chlamydial infections in children. These antimicrobials, usually sulfonamides, macrolides, and tetracyclines, are the most common agents; tetracyclines should not be administered to children under the age of 8 years because of the resulting dental discoloration that may occur. Oral erythromycin therapy (50 mg/kg/day in four divided doses administered for 14 days) has been recommended for both neonatal inclusion conjunctivitis and chlamydial pneumonia. Sulfonamide antimicrobials are an acceptable alternative in infants at least 3–4 weeks old. Azithromycin is considered by many to be the treatment of choice of *C. trachomatis* genitourinary infection because it may be administered as a single-dose treatment. Doxcycline, a tetracycline antimicrobial, is typically given for a 1-week course. Erythromycin and ampicillin are alternative options for pregnant women with active chlamydial infections.

Inflammatory Hemorrhagic Cystitis (Viral Cystitis)

Viral cystitis causes irritative voiding symptoms and hematuria in infants and children. In the toilet-trained older child, it is characterized by symptoms of urinary frequency, urgency, dysuria, incontinence, and gross hematuria with a negative urine culture for bacterial organisms. Severe hemorrhagic viral cystitis is seen more frequently in immunosuppressed pediatric patients, most commonly those who have undergone HSCT or children infected with HIV. Viral infections can often be life threatening in these immunocompromised patients. The incidence rate of hemorrhagic cystitis in the HSCT pediatric population has been cited to range from 10% to 70%.[43]

The usual causative viruses are adenovirus types 11 and 21, influenza A, polyoma BK virus, and cytomegalovirus. Adenoviruses are a family of double-stranded, nonenveloped DNA viruses transmitted through droplet and fecal–oral spread. Adenovirus infections, in the form of asymptomatic or mild self-limited respiratory infection, are exceedingly common in the general pediatric population. In the immunocompromised host, however, adenovirus can cause severe localized disease manifestation, including pneumonitis, hepatitis, colitis, and severe hemorrhagic cystitis.[44] At present, adenovirus is the most common cause of viral hemorrhagic cystitis in immunocompromised children. In study populations, male patients outnumber female patients by a ratio of 2–3:1. It may occur as a result of a new exposure causing a primary infection or reactivation of latent disease. Viral shedding may continue throughout the duration of the illness, lasting a median duration of 2 weeks (range 1–111 days).[45]

There are a number of clinical tests available for the specific diagnosis of adenovirus infection. Nearly all adenovirus serotypes cause a distinct cytopathic effect (CPE) in human epithelial cell lines, and thus can be detected by routine viral culture from collected urine specimen. Direct detection of adenovirus antigens in clinical samples may be performed by an adenovirus-specific ELISA or immunofluorescence assay. These assays are more rapid but less sensitive than viral culture for the detection of most serotypes and have been shown to be less sensitive in the immunocompromised population. Quantitative PCR in blood and urine has been increasingly utilized in pediatric HSCT patients, both for diagnosis and to assess response to treatment. Radiographic changes within the bladder are remarkable and often resemble that of a bladder sarcoma, and ultrasonography may show a diffusely thickened bladder wall (Figure 8.14).

Human polyoma BK virus belongs to the genus *Polyomaviridae*, which consists of nonenveloped DNA

FIGURE 8.14 Inflammatory hemorrhagic cystitis—diffusely thickened bladder wall. (Courtesy of Wong-You-Cheong JJ et al. *Radiographics* 2006;26:1847–68.)

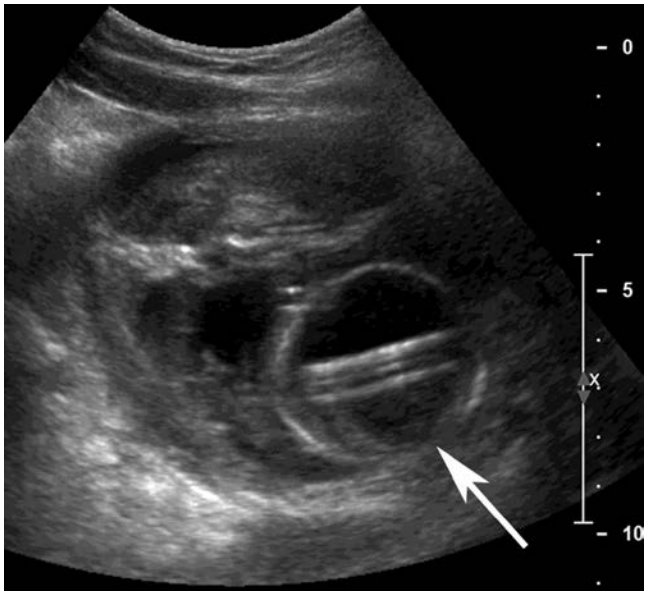

FIGURE 8.15 Bone marrow transplantation patient with diffuse bladder thickening and extensive intraluminal clot. (Courtesy of Hollingsworth CL et al. *Radiology* 2008;248:348–65.)

viruses. It is a ubiquitous virus, present in nearly 80% of the population. Primary infection is usually asymptomatic. BK virus is frequently identified in the urine of HSCT patients with hemorrhagic cystitis.[46] The diagnosis of BK viruria is made by identification of epithelial cells within the urine containing intranuclear inclusion bodies suggestive of BK virus and a positive PCR test for BK virus in the urine. Arthur et al.[47] report that the viruria occurred exclusively in patients who were seropositive at transplantation, indicating a reactivation of the latent virus from dormant sites. BK viremia has also been correlated quantitatively with posttransplant hemorrhagic cystitis. Patients with plasma BK virus greater than 104 copies/mL appeared to be at higher risk of viral hemorrhagic cystitis. Many immunocompromised patients do not respond to traditional therapies for hemorrhagic cystitis and may develop extensive and recalcitrant clot retention (Figure 8.15) and ultimately progress to acute renal failure.

Different strategies have been advocated for the management of severe intractable viral hemorrhagic cystitis. Treatment recommendations are often based on experience from case reports or small series studies. In mild cases, treatment may begin with aggressive fluid hydration, pyridium for analgesia, and forced diuresis with furosemide. In all patients with severe hemorrhagic cystitis, correction of thrombocytopenia and coagulopathy is imperative, and may decrease the severity of the hematuria. The use of several antiviral agents, such as ribavirin, ganciclovir, and cidofevir, as well as human leukocyte transfusions, has all been reported in the literature.[45] Ribavirin, an intravenous antiviral agent, has had the greatest reported success in children with acute adenovirus hemorrhagic cystitis. Renal excretion, accounting for nearly one-third of the drug's elimination, ensures high levels of ribavirin in renal and bladder tissues.[44] Its most common side effect is a mild reversible anemia. Cidofevir has been used in both intravenous and intravesical administrations. The most common side effect, nephrotoxicity and resultant renal failure, has hampered its systemic use in the bone marrow transplantation population. Case reports of intravesical instillation of cidofevir (5 mg/kg diluted in 100 mL of saline, slowly instilled via a Foley catheter, which is clamped for 1 hour, BID) have demonstrated marked reduction in hematuria and clearance of the virus on subsequent urinary PCR testing.[48]

Continuous bladder irrigation with saline has also been used in cases of hematuria with clot retention. Several compounds, alum, phenol, silver nitrate, formalin, and prostaglandins, have been tried in intravesical instillation regimens. Aluminum toxicity and long-term complications of formalin instillation, which include bladder fibrosis, urinary frequency and/or incontinence, vesicoureteric reflux, and obstruction, make these instillations less desirable options. Prostaglandins have been advocated due to their role in vasoconstriction and platelet aggregation of the vascular epithelium, their cytoprotective effect on bladder mucosa, and their low toxicity and good tolerability profile. Cesaro et al., in a large multicenter pediatric retrospective study, showed the beneficial effects of hyperbaric oxygen therapy (HOT) in severe, refractory cases of viral hemorrhagic cystitis.[49] Cystotomy, cystoscopy with clot evacuation, vesicostomy, and even cystectomy with urinary diversion or vesical artery embolization are treatments reserved for refractory life-threatening cases only.

Eosinophilic Cystitis

EC is a rare inflammatory disorder of the urinary bladder, characterized by irritative voiding symptoms. There are less than 30 pediatric case reports in the reported literature. The disease is characterized by a transmural

inflammation of the bladder wall predominated by eosinophils, and fibrotic changes with or without muscle necrosis. Symptoms are nonspecific, with the most common being dysuria, frequency, hematuria, and suprapubic discomfort.[50] Children may present with a palpable suprapubic mass on physical examination. Occasionally, this may be mistaken for an invasive bladder tumor or pelvic sarcoma.[51] EC has been reported to occur in all age groups, with a slight male preponderance in children. Associated conditions include history of allergy, asthma, atopy, history of bladder trauma, bladder surgery, parasitic infections, autoimmune disorders, and intravesical chemotherapy.

The true etiology of EC remains unknown. An immunoglobulin E (IgE)–mediated allergic cause has been suggested given the strong allergic histories of these patients. Food allergens, drugs, and other substances have been implicated.[52] It has been postulated that various inciting agents, such as bacteria and foreign protein, act as antigenic stimuli in the bladder to produce an eosinophilic infiltration. These antigens form immune complexes, resulting in the release of enzymes and cytokines that enhance the inflammatory cascade and its resultant bladder tissue damage.

Typical presentations are characterized by irritative voiding complaints, dysuria, frequency, hematuria, and suprapubic pain. Less common symptoms include nocturia and urinary retention.

Rare presentations include gastrointestinal symptomatology due to eosinophilic gastroenteritis.[53] Physical examination is usually unremarkable, with the exception of rare cases of children presenting with palpable lower abdominal masses. Urinalysis commonly shows proteinuria, pyuria, and microscopic hematuria. Eosinophils in the urine or peripheral blood eosinophilia, although diagnostically helpful, are infrequently found. Elevated serum levels of IgE have been reported in the literature.[54] Urine cultures are typically negative.

Imaging studies of the bladder usually begin with ultrasonography. Irregular focal or diffuse thickening of the bladder wall may be evident, as well as hydronephrosis, hydroureter, and infiltrative bladder masses. A cystic form of EC may be seen as well (Figure 8.16).[25] The definitive diagnosis is established by cystoscopy and bladder biopsy. Cystoscopic findings include erythematous, velvety, raised plaques. The mucosa is often edematous with areas of ulceration.[53] These findings are nonspecific and may be confused with other forms of cystitis and neoplastic conditions, such as interstitial cystitis, tubercular cystitis, carcinoma in situ, and bladder rhabdomyosarcoma. Tamai et al. reported the MRI findings of a young girl with EC, being characterized by near-circumferential thickening of the bladder wall with relative sparing of the dome, and distinctly low-signal intensity on T2-weighted series consistent with fibrosis and increased tissue cellularity.[55]

Bladder biopsy shows a classic eosinophilic infiltration predominantly in the lamina propria, as well as the deeper muscle layers of the bladder wall (Figure 8.17). There may be focal muscle necrosis or significant detrusor fibrosis, resulting in a contracted bladder. Giemsa stain for eosinophils and trichrome stain for muscle fibrosis are helpful in making the diagnosis.[56] Electron microscopy is also a useful diagnostic aid.

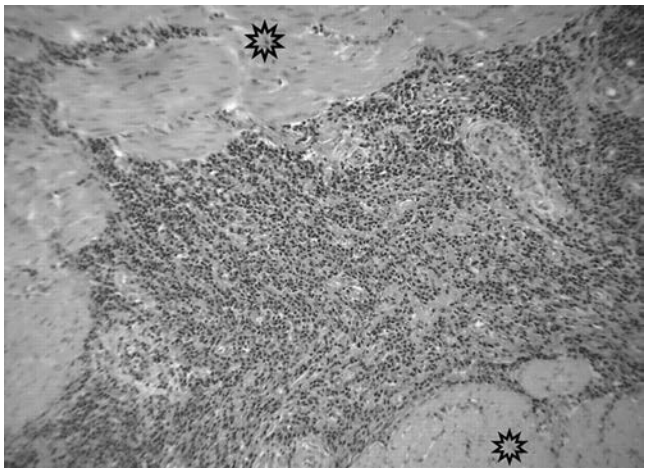

FIGURE 8.16 EC. Photomicrograph demonstrating an intense infiltration of eosinophils deep within the muscularis propria. (Courtesy of Wong-You-Cheong JJ et al. *Radiographics* 2006;26:1847–68.)

The treatment of EC involves removing the antigenic stimulus, if present and identifiable. A formal allergen skin test may aid in the identification of the antigenic stimulus

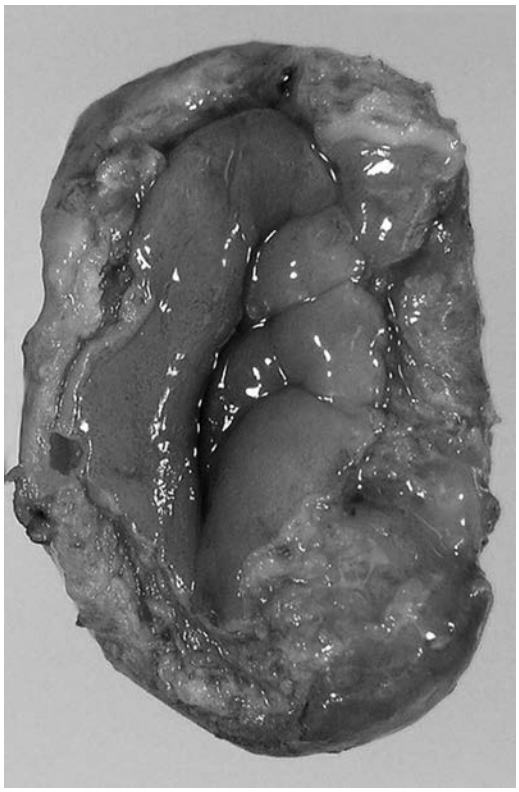

FIGURE 8.17 EC. Bladder gross specimen, cut section, demonstrating circumferentially thickened bladder wall. (Courtesy of Wong-You-Cheong JJ et al. *Radiographics* 2006;26:1847–68.)

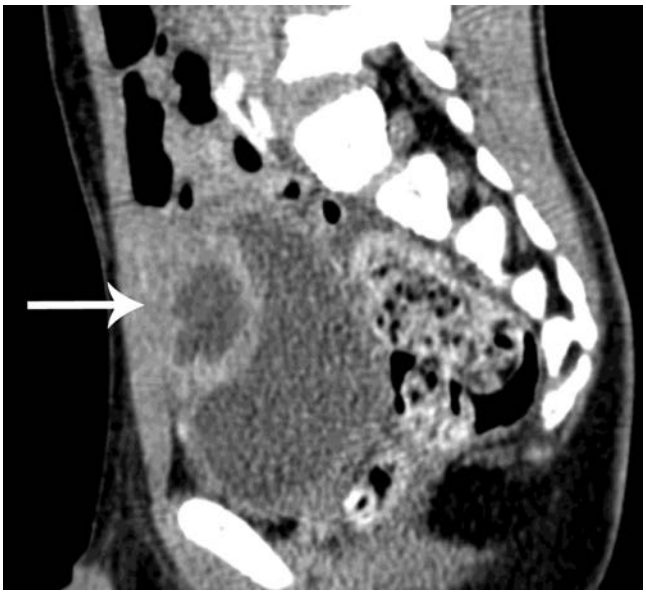

FIGURE 8.18 EC. Contrast-enhanced CT images show a thick-walled cystic mass (arrow) arising from the anterior dome of the bladder. (Courtesy of Wong-You-Cheong JJ et al. *Radiographics* 2006;26:1847–68.)

in the pediatric population. When no obvious cause is identified, initial management with nonsteroidal anti-inflammatory drugs, as well as antihistamines, has been used with good results. Patients who show no response to these agents have also been successfully treated with oral corticosteroids. Other case reports cite success with alternative agents, including silver nitrate and cyclosporin A.[53] Refractory cases with resultant bladder fibrosis and obstructive uropathy are quite rare, but have necessitated more radical therapy with partial cystectomy and bladder augmentation (Figure 8.18).[57]

The prognosis for children with EC is generally very good. Almost all reported cases in the literature resolved within 12 weeks. Despite the apparent self-limited course of EC, it should be kept in mind that recurrence and even unremitting progression of this disease are possible. Documented recurrences have been reported several years after the initial event. It has been hypothesized that local surgical trauma to the bladder may be the cause for recurrence. A recommendation for pretreatment with steroids and antihistamines prior to bladder surgery has been made for patients with a previous history of EC.[58]

Malacoplakia

Malacoplakia is a rare benign chronic inflammatory condition thought to be a consequence of a defective phagolysosomal system. It was first described by Michaelis and Gutmann in 1902. It clinically manifests as single or multiple plaque-like tumors that may appear in any organ system. The name *malacoplakia* is derived from the Greek words *malakos* and *plakos*, meaning soft and plaque. In the adult population, malacoplakia affects the bladder in about 40% of cases.[59] Conversely, in the pediatric population, a wide variety of organs, such as the

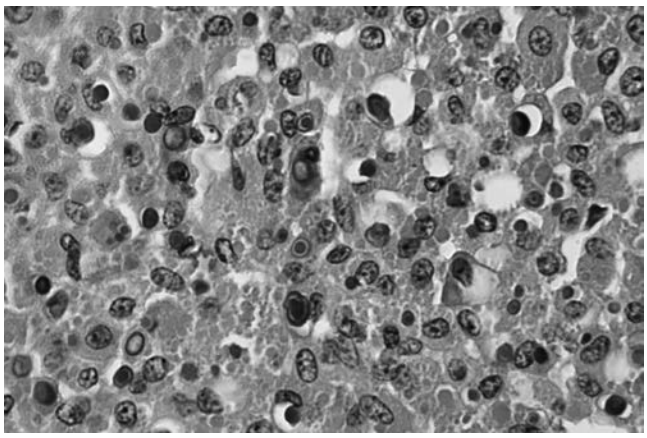

FIGURE 8.19 Malacoplakia. Micrograph demonstrating Michaelis–Gutmann bodies, the pathognomonic finding on microscopy with hematoxylin and eosin (H&E) staining. (Courtesy of WikiMedia Commons, online repository of freely licensed media.)

tongue, gastrointestinal tract, lungs, brain, adrenals, and retroperitoneum, may be involved, but the most common genitourinary site appears to be the kidney.

It has been postulated that the cause is the defective digestion of phagocytosed bacteria due to an intracellular abnormality of macrophage function.[60] Microscopically, malacoplakia consists of large macrophages mixed with lymphocytes and plasma cells. The pathognomonic feature is the rounded intracytoplasmic inclusions, which contain incompletely digested bacterial components mineralized with iron and calcium phosphate salts. These Michaelis–Gutmann bodies are evident on histologic evaluation by their characteristic concentric "owl-eye" appearance (Figure 8.19).

Pediatric genitourinary malacoplakia is quite rare, with very few published case reports in the current pediatric literature. It typically occurs in the setting of recurrent UTIs, usually with *Escherichia coli*.[59] The female-to-male incidence of disease is approximately 4:1. Malacoplakia more often presents in immunocompromised patients, in the setting of renal transplantation, diabetes mellitus, lymphoma, and chronic corticosteroid use, and is often quite resistant to treatment in these populations. Rare case reports document pediatric presentations characterized by symptoms of urinary frequency, dysuria, and recurrent UTIs.[61] Clinically, the lesions of malacoplakia are described as yellowish, polypoid smooth papules, plaques, or nodules with peripheral hyperemia. Draining abscesses and sinus tracts have been reported to occur near the urethra, testes, vulva, and perineum. Renal malacoplakia is suspected in the pediatric patient when response to traditional antimicrobial therapy does not occur. These patients often have persistent nephromegaly without abscesses demonstrated by either ultrasonography or CT. Although renal parenchymal malacoplakia is extremely rare in children, sonography is usually the first imaging modality used for diagnosis of this condition. Sonographic and CT features are generally nonspecific and include circumferential bladder thickening, polypoid bladder

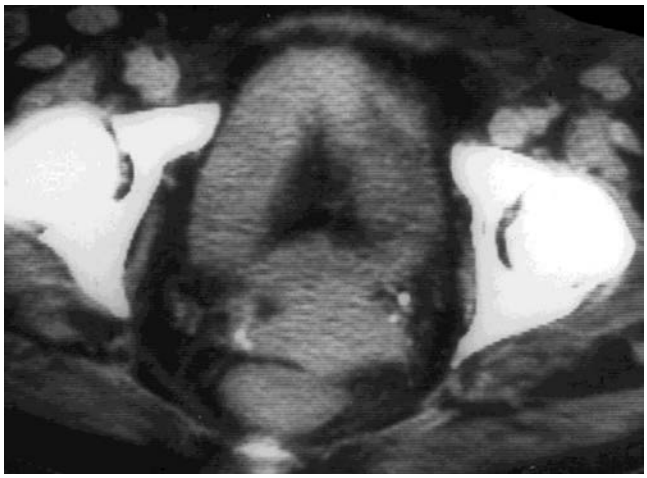

FIGURE 8.20 Malacoplakia. Axial CT demonstrating circumferential bladder wall thickening. (Courtesy of Wong-You-Cheong JJ et al. *Radiographics* 2006;26:1847–68.)

masses, enlarged kidneys, focal hypoechoic masses, and heterogeneous masses with areas of necrosis (Figure 8.20). The renal lesions may be confused with focal nephritis, renal tumors, or lobar nephronia due to these nonspecific features. MRI of renal malacoplakia may show single or multiple nodules with low signal on T1-weighted, T2-weighted, and early and late postgadolinium images.[62] Diagnosis is usually confirmed by renal biopsy (either open or percutaneous), showing chronic parenchymal inflammation with Michaelis–Gutmann bodies. Reports have confirmed the diagnosis by cytologic evaluation of a renal fine-needle aspirate.[63]

Previously, bilateral renal malacoplakia in the pediatric population was considered a fatal disease. Unilateral disease was frequently treated with nephrectomy. Bladder lesions have also been treated with transurethral resection. Patients should receive antimicrobial therapy using an antimicrobial agent with intracellular activity (i.e., trimethoprim-sulfamethoxazole and quinolones), or with immunomodulating pulse therapy with methylprednisolone and intravenous granulocyte colony-stimulating factor (G-CSF). If a patient is on immunosuppressive therapy, a reduction in the immunosuppressive regimen is recommended. With the advent of such treatment, nephrectomy is rarely necessary to treat renal malacoplakia in the pediatric population.

OTHER INFLAMMATORY DISEASES OF THE GENITOURINARY TRACT

Epididymitis, epididymo-orchitis, and orchitis

Epididymitis has been increasingly reported as a cause of acute scrotum in the pediatric population. It results from an inflammatory reaction of the epididymis to an infectious agent, a chemical irritant, or a nonspecific cause. Epididymitis is typically idiopathic, but it can be associated with UTIs, autoimmune disease, trauma, or urinary tract abnormalities (UTAs).[64] Although infection with bacteria or viral organisms is traditionally thought to be the cause of epididymitis, the majority of documented cases are not associated with culture-proven UTIs.[65] Sterile urine in the epididymis may also be sufficient to incite an inflammatory reaction. Epididymal infection may therefore occur as a result of retrograde passage of urine through the ejaculatory ducts, hematogenous spread from a systemic infection, or direct extension from a preexisting orchitis.

Boys with epididymitis usually present with scrotal pain of gradual onset, scrotal erythema, and edema. They are typically exquisitely tender to palpation in the region of the epididymis and the vas deferens. A reactive hydrocele may also be present on exam. The differential diagnosis of epididymitis in a child must always include testicular torsion, torsion of an appendix testis, and idiopathic scrotal edema. A clue to the diagnosis is often the more insidious onset of pain in boys with epididymitis than in boys with torsion events. Careful physical examination and radiologic imaging studies with Doppler ultrasound will often aid in making the correct diagnosis (Figure 8.21).[66] If a definitive diagnosis of epididymitis cannot be arrived at, then surgical exploration may be required to exclude testicular torsion.

The use of a urinalysis in making the diagnosis of epididymitis is often inconclusive. Gislason et al. showed that less than 25% of patients with epididymitis had greater than 10 white blood cells per high-power field on urinalysis at the time of presentation.[67] Graumann et al. studied a cohort of 151 consecutive patients, of which only 1 (1%) demonstrated bacteriuria in his urinalysis.[68] Urinalyses have also been abnormal in 10% of boys that present with testicular torsion. Urine cultures are also unrewarding in making the diagnosis of epididymitis, as only 12% were positive in the cohort of boys with epididymitis that were retrospectively studied by Gislason et al.[67]

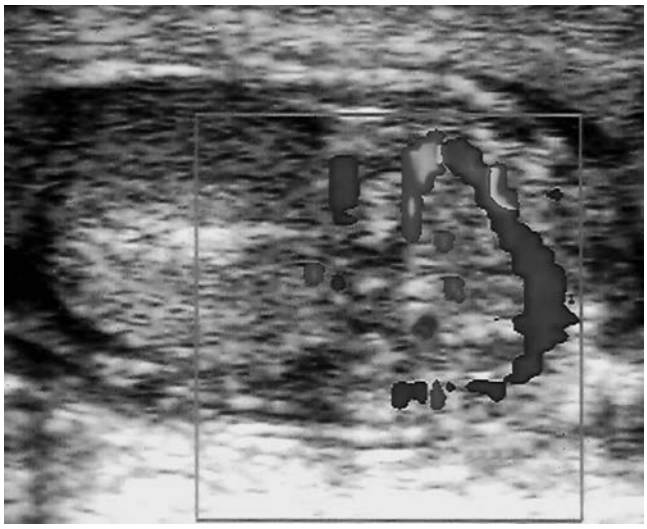

FIGURE 8.21 Acute epididymitis. Ultrasound demonstrating thickened, hyperemic epididymal tail with increased Doppler flow. (Courtesy of Woodward PJ et al. *Radiographics* 2003;23:215–40.)

The evaluation of a boy with epididymitis should not end once the immediate diagnosis has been confirmed. This relatively rare problem in boys is often enigmatic in its etiology. In prepubertal boys, infection in the epididymis may result from a variety of UTAs, such as neurogenic bladder, dysfunctional voiding, urethral obstruction (posterior urethral valves or meatal stenosis), or an ectopic ureter draining into the seminal vesicle or vas deferens.[64] Children with these anomalies more commonly have recurrent or chronic epididymitis, making the recognition of these entities even more important to preventing disease in this population.

Investigational procedures after resolution of the inflammation should be performed. Urologists vary widely in their recommendations for radiologic examinations. Most agree that at a minimum, an upper tract evaluation with a renal bladder ultrasound should be performed for culture-proven bacterial epididymitis. In young children, excretory urography (intravenous pyelography [IVP]) is the imaging study of choice to identify an ectopic ureter draining to the seminal vesicles, while a voiding cystourethrography (VCUG) would demonstrate urethral anomalies and reflux of urine into the ejaculatory ducts (Figure 8.22).[69]

Both neurogenic bladder and dysfunctional voiding have been found to be associated with acute epididymitis. Spasm of the external sphincter is thought to facilitate retrograde urine flow through the vas deferens and ejaculatory ducts. Bukowski et al. found that in a series of 56 boys with epididymitis, nearly 25% had dysfunctional voiding tendencies associated with epididymitis.[70]

Therefore, the addition of a detailed voiding history and use of noninvasive urodynamic testing with uroflow, patch electromyography, and postvoid residual urine assessment have been advocated for boys over the age of 5 years that present with epididymitis. Congenital urologic anomalies are a less frequent cause of epididymitis in the absence of documented bacterial infection.

The treatment of acute epididymitis includes scrotal support and elevation, and analgesic and anti-inflammatory medications. Given the reportedly low incidence of UTIs in boys with epididymitis, antibiotics can be reserved for young infants and those with pyuria or positive urine cultures.[71] Once the acute infection is treated, age-appropriate studies to determine the etiology of the epididymitis should be undertaken.

Vulvovaginitis

Vulvovaginal inflammation is the most common gynecologic complaint of the prepubertal girl. Most cases are initially treated by the primary pediatrician, with subsequent referral to the pediatric urologist or gynecologist only when symptoms persist. Vulvovaginitis is most commonly seen in prepubertal females between the ages of 2 and 7 years. The child is typically brought to the physician with complaints of foul vaginal discharge, discomfort, pruritus, and urinary symptoms such as burning with voiding. The parents may note a discharge present in the child's diaper or undergarments. An abnormal odor and/or redness of the vulva may also be described.

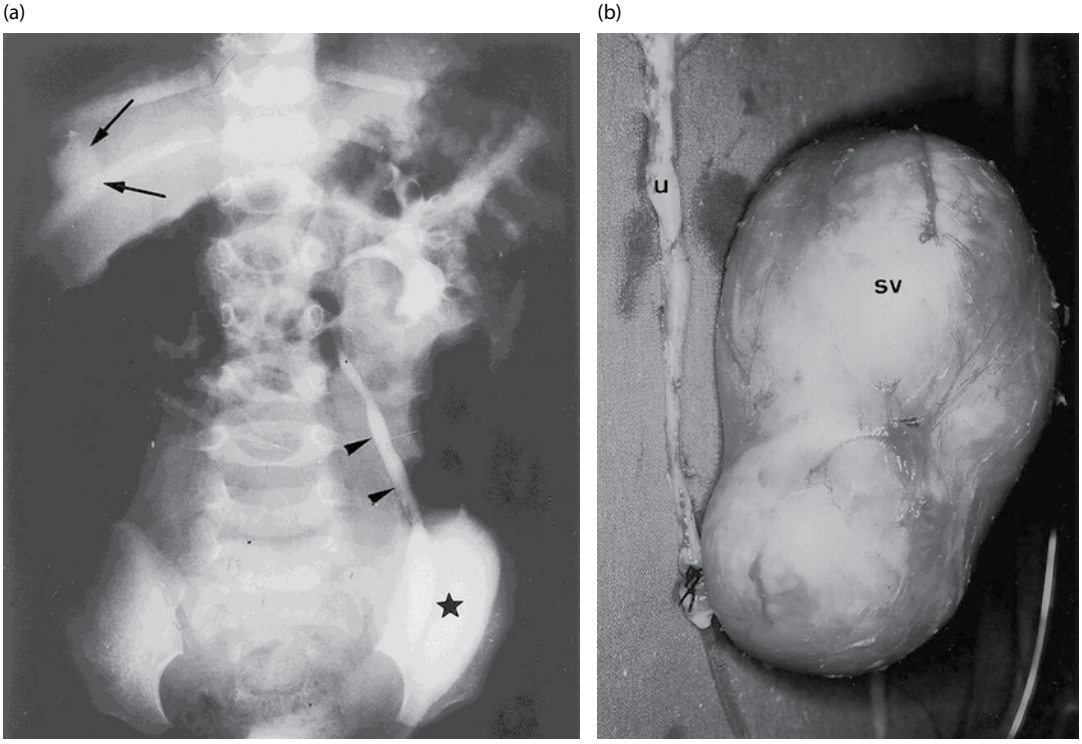

FIGURE 8.22 (a) Intravenous urogram demonstrating left ectopic ureter draining to seminal vesicle and thus displacing the bladder to the left. (b) Gross specimen of ectopic ureter (u) draining to markedly dilated seminal vesicle (sv). (Courtesy of Berrocal T et al. *Radiographics* 2002;22:1139–64.)

Vaginal discharge is physiologic in female neonates. The majority of newborn girls have a clear, white, odorless vaginal discharge during the newborn period that is primarily a response to the perinatal stimulation of circulating maternal estrogens.[72] This should not be mistaken for a pathologic process. At puberty, both the vulvar and vaginal tissues are once again stimulated by circulating estrogens, and therefore swelling and discharge may be expected.

There are several reasons to explain why young girls are particularly susceptible to vulvovaginitis. Anatomically, the vulva of the young girl is relatively unprotected, lacking the natural barrier to infection of the labial fat pads and pubic hair of the postpubertal girl. Vulvar skin is also thin, sensitive, and easily irritated by minor trauma. In addition, the vaginal mucosa is also thin at this age. The vaginal cavity in these prepubertal girls is also an excellent culture medium for bacteria with its neutral pH and warm, moist environment. Finally, the close proximity of the anus allows easy transfer of bowel organisms, particularly in this age group. These obvious structural and biologic differences make the vulvovaginal environment of prepubertal girls particularly sensitive to inflammation. In addition, children tend to have poor hygiene habits compared with adolescents. They do not practice good handwashing and often play in areas that expose them to dirt and sand, creating chronic irritation of the vulva. The presence of a foreign body or suspected sexual abuse must also be considered in the list of risk factors for vulvovaginitis in the prepubertal girl.[73]

In evaluating the young child with vulvovaginitis, the preceding risk factors should be kept in mind. A complete history and detailed perineal examination must be performed. The history should include information concerning the onset of the condition and any therapies previously instituted for treatment. A history of potential chemical irritants should be elicited (i.e., bubble baths, soaps, and powders). A previous surgical history and family history of diabetes, eczema, or contact sensitivities should be addressed. The child's social setting should also be reviewed for information regarding potential child abuse (i.e., primary caregiver, day care, and contact with older children). The physical examination should look for evidence of chronic illness, dermatologic problems, or traumatic injury. Most girls can be comfortably examined either lying supine in their mother's lap or in the frog-leg position. Some sexual abuse experts recommend a knee–chest position for a complete examination. Cultures may be obtained by a sterile saline-moistened swab or a saline flush of the vaginal introitus. If bleeding or malodorous discharge raises the issue of a foreign body, then formal vaginoscopy may need to be undertaken under anesthesia. If a persistent and continuous flow from the vaginal introitus is present, then an ectopic ureter may enter the differential diagnosis. In this situation, ultrasonography or VCUG will assist in confirming the diagnosis.

Malodorous discharge with associated vaginal bleeding should alert the clinician to the possibility of the presence of a foreign body within the vagina. Eighty percent of all foreign bodies present within the vagina are wads of toilet tissue lodged in the vaginal canal.[74] This may result in both an infectious and an inflammatory response. Various other foreign bodies have been recovered, including coins, safety pins, pen tops, and small toys. The probability of foreign bodies being recovered from the vagina of prepubertal girls presenting with vulvovaginitis is 4%.[75] The inflammatory response associated with the presence of the foreign body resolves with the removal of the object.

The treatment of vulvovaginitis depends entirely on the etiology of the inflammation. Nonspecific vaginitis accounts for the majority of these prepubertal cases. It is thought to involve alterations in the normal flora of the vagina, resulting in vulvar and distal vaginal inflammation. The vagina of a prepubertal girl is typically colonized with the same variety of bacteria as observed in older women. A study by Gerstner et al. found that swabs from 75% of these girls grew aerobic bacteria, 65% showed anaerobic bacteria, and 45% grew both. The specific organisms identified were *Staphylococcus epidermis* (35%), enterococci (29%), *Streptococcus viridans* (13%), and lactobacilli (39%).[76] It therefore may be appropriate to request colony counts on all organisms recovered from culture, as overgrowth by one particular organism may warrant antimicrobial therapy directed at that organism. Routine treatment of nonspecific vaginitis is usually directed toward improved hygiene, avoidance of irritating stimuli, treatment of concurrent constipation, and techniques to promote drying of the vulva, such as wearing loose-fitting clothing at night.

Specific vaginitis in prepubertal girls may be the result of infections with *C. albicans* and *E. vermicularis*. Treatments of these infections have been previously outlined in this chapter. Other causes of specific vaginitis include sexually transmitted organisms, resulting in gonorrhea, chlamydia, and herpes. The treatment of these infections is outlined in Table 8.1. These organisms may be acquired during passage of the newborn through the birth canal or may result from sexual abuse. The age at presentation, along with social history and physical examination, will suggest the etiology.

Interstitial Cystitis

Interstitial cystitis is a chronic, debilitating bladder disease of unknown etiology that is seldom reported to occur in children. The first report of the disease was made by Skene in 1878.[77] Since that initial report, there have been only a handful of case reports that document this disease specifically in the pediatric population.

TABLE 8.1 Treatment of specific vulvovaginitis

Specific infection	Treatments
Gonorrhea	Penicillin G, tetracycline, ceftriaxone, cefixime, erythromycin
Chlamydia	Azithromycin, doxycycline, erythromycin
Gardnerella vaginalis	Metronidazole
Herpes	Acyclovir

Patients with interstitial cystitis typically have severe sensory urgency with urinary frequency and bladder pain that may be ameliorated with voiding. Cystoscopy after hydrodistention in these patients will classically show changes varying from petechial hemorrhage to other regions with classic Hunner's ulcers.[78] The majority of patients with interstitial cystitis are middle-aged women. The disease is less frequently reported in men and very rarely documented in children.

Chenoweth and Clawater were the first to report interstitial cystitis in children.[79] In their series of seven cases, they describe the presenting signs and symptoms as diurnal and nocturnal urinary frequency, abdominal pain, and decreased bladder capacity in the context of a negative urinalysis and culture. In addition, these children were described as being extremely anxious and easily upset and having poor appetites. Farkas et al. report that the pediatric cases of interstitial cystitis are more common in adolescent girls.[80]

Close et al. reported the first large retrospective analysis of interstitial cystitis in the pediatric population, distinguishing this disease process with voiding dysfunction.[78] They characterized a cohort of 16 individuals who presented over a 12-year period. Unlike previous pediatric and adult reports, there is less of a female preponderance, with 70% girls and 30% boys in the study population. The most common presenting symptom was urinary frequency and urgency (88%), followed by abdominal pain relieved by voiding (81%). All patients had negative urinalysis and urine culture.

Diagnostic evaluation of pediatric patients suspected of having interstitial cystitis consists of cystoscopy with hydrodistention. Cystoscopically, patients typically have diffuse glomerulations and terminal hematuria after hydrodistention (Figure 8.23). Bladder biopsies, obtained in select cases, classically reveal chronic inflammation with lymphocytic infiltrate. No mast cells or eosinophils are generally noted. Urodynamic evaluation demonstrated early bladder filling sensation with no evidence of involuntary bladder contractions. Bladder capacity is also significantly reduced in these individuals.

Treatment of interstitial cystitis in children is met with the same disappointing results as in adults. Bladder distention may temporarily alleviate symptoms. Repeated hydrodistentions were required by 50% of the patients reported by Close et al.[78] As in the adult population, clorpactin instillations have also been utilized with temporary and often incomplete relief of symptoms. Although intestinal bladder augmentation has been reported as a last-resort treatment option, inflammatory changes consistent with

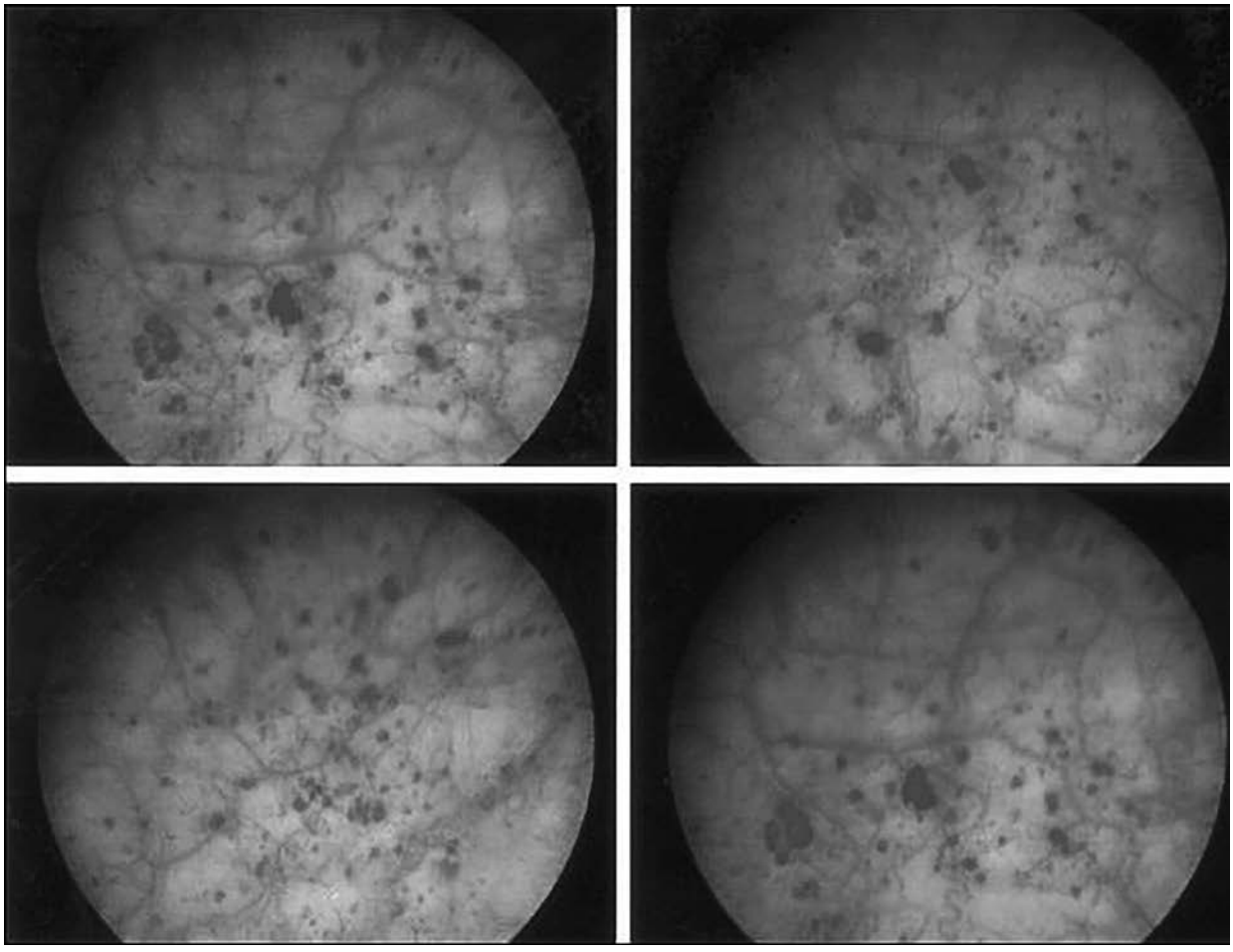

FIGURE 8.23 Interstitial cystitis. Classic appearance of bladder glomerulations after cysto-hydrodistention.

interstitial cystitis have been found in the bowel segments on follow-up. Surgical management of this disease in children should be considered only when all other treatment options have failed and the diagnosis has been absolutely confirmed.

Idiopathic Scrotal and Penile Edema

Acute idiopathic scrotal edema (AISE) is a rare, self-limited clinical entity characterized by genital erythema, edema, and painful scrotal swelling. This is a distinct diagnosis that may be responsible for up to 20% of cases of acute scrotal inflammation.[65] It is important to distinguish this diagnosis from more common causes of acute scrotal swelling, such as testicular torsion, torsion of the appendix testis, epididymo-orchitis, acute hydrocele, or incarcerated inguinal hernia.

The largest single series of idiopathic scrotal edema was reported by Klin et al. in 2002, in which they retrospectively reviewed 38 patients, with 44 episodes of AISE over a 10-year study period.[81] The average age of presentation was 6.2 years (range 2–12 years). Ninety percent of the patients exhibited unilateral involvement, typically with a sudden onset of scrotal erythema and edema, which was minimally tender. Perineal, abdominal, and inguinal extension of the erythema were present in more than 50%.

There has been much speculation as to the etiology of AISE. Suggested etiologies have included infection, insect bites, allergy, mild scrotal trauma, and urinary extravasation. Infection with cellulitis was thought to be the etiology until multiple studies revealed negative intraoperative cultures, no elevation of peripheral white blood cell count, and normal urinalysis and culture.[82] The process is also self-limiting and resolves without the use of antibiotics. Insect bites were also entertained as an etiology; however, the lack of a lesion characteristic of a bite has made this less likely. Allergy has also been suggested as an etiology, especially given the presence of eosinophilia, asthma, eczema, and dermatitis in select cases. In no case, however, has a particular allergen been identified, and the majority of these patients are not characterized as having an allergic diathesis.[83]

AISE typically presents in prepubertal boys between the ages of 5 and 11 years. The children characteristically present with a less than 24-hour history of acute penile and scrotal erythema, edema, swelling, and mild pain (Figure 8.24). Inguinal, perineal, and penile involvement have been reported to occur in up to 60% of cases. The children are frequently afebrile with normal ancillary testing, including urinalysis, and peripheral white blood cell count. Occasionally, eosinophilia is present. When examined early in the process of scrotal swelling, the spermatic cord and testes should feel normal. Characteristically, the clinical findings resolve in 1–2 days. Kaplan reported that in his series of six patients, the examiner had the distinct impression that the edema was confined to the superficial layers of the scrotum, and that it rarely extended to the penis.[83] Lau and Ong reported that a similar benign and self-limiting edematous condition of the penis exists that is suspected to be a variant of idiopathic scrotal edema.[84]

FIGURE 8.24 Acute idiopathic penile and scrotal edema, seen in a 17-year-old boy. (Courtesy of the Pediatric Urology Department of Lucile Packard Children's Hospital, Palo Alto, California.)

If the diagnosis is uncertain, which it often is given the similarity to many emergent causes of acute scrotum, then diagnostic imaging studies may be necessary. Testicular ultrasound is most commonly utilized to differentiate these pathologies. Classic sonographic features include marked thickening of the scrotal wall, with heterogeneous striated and edematous appearance; increased peritesticular blood flow; and at times a mild reactive hydrocele (Figure 8.25).[85]

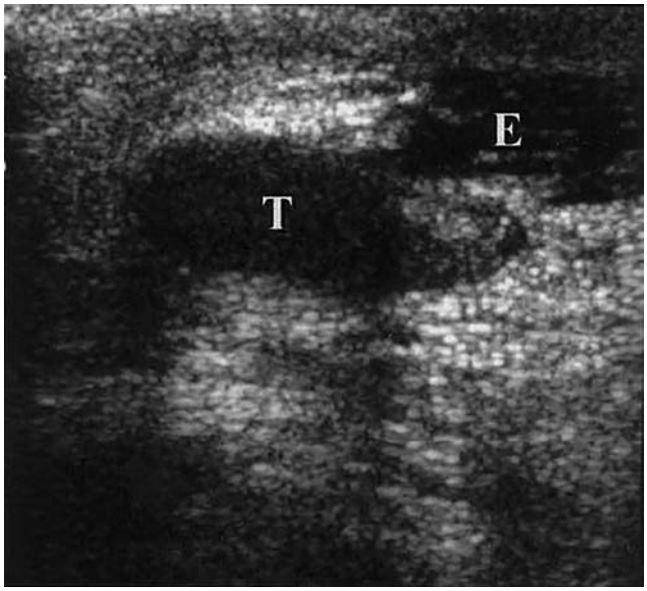

FIGURE 8.25 AISE. Scrotal ultrasound demonstrating markedly thickened scrotal wall with striated, edematous tissue. T, Testis and E, Epididymis. (Courtesy of Klin B et al. *J Pediatr Surg* 2002;37:1200–2.)

Radionuclide testicular scanning or Doppler ultrasonography may be necessary to exclude testicular pathology. On physical examination, this can often be assessed by manipulation of the testis into the superficial inguinal pouch, where it can be noted to be palpably normal and nontender. In rare instances, when diagnostic uncertainty still exists, surgical exploration to rule out testicular pathology will reveal a normal testis and epididymis with inflammation confined to the scrotal wall.

Interestingly, there have been case reports of scrotal edema as a presenting symptom in certain systemic disorders, such as sarcoidosis and inflammatory bowel disease. In Klin et al., sigmoidoscopy was performed to rule out inflammatory bowel disease as the underlying etiology.[81]

Evans and Snyder suggest that idiopathic scrotal edema bears a strong resemblance to angioedema, which is characterized by a localized painless swelling of the subcutaneous tissue of various body parts.[82] The overlying skin is usually normal in color and temperature, but slightly erythematous. Angioedema results from a dilation of small blood vessels, with a transudation of fluid through the capillaries. These vascular changes are believed to be mediated by a local derangement of histamine release. Recommended therapy should consist of reassurance and perhaps a short course of antihistamines.

AISE is nearly always a self-limiting disease. Appropriate management includes reassurance, scrotal support, and close observation. Nonsteroidal anti-inflammatory drugs, antihistamines, or antibiotics may be used as the diagnosis is developed. If the diagnosis is ever in doubt after appropriate clinical, laboratory, and imaging evaluation, then surgical exploration and biopsy may be necessary to rule out nonbenign etiologies.

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CHAPTER
9

Anesthesia and Pain Management for the Pediatric Urology Patient

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CONSIDERING THE WHOLE PATIENT

The pediatric patient who presents for urologic evaluation, consultation, management, and/or surgery should be approached and treated with immense sensitivity. The urologic problem may be just one of a number of associated congenital problems, part of a syndrome, association, or sequence, placing the patient at risk for a series of interventions and/or operations over a lifetime, an ongoing challenge even for a very high-functioning patient. The urological problem may be something incidental to a syndrome, association, or sequence that has other major defining features, or it may be the main feature of the syndrome, association, or sequence. An isolated congenital problem may in itself be associated with the need for serial procedures and/or operations. The urologic problem may be associated with cancer, may be a sequel to another disease process, or may be associated with trauma or a traumatic event, any of which may necessitate serial interventions and exact emotional trauma on a patient and his or her family.

In any case, the urogenital system is both highly personal to each patient and his or her family and immensely essential to both identity and normal physiologic function. Thus, the whole patient and his or her family must be considered, evaluated, and treated appropriately. Any and all events of physiological, physical, psychological, or emotional harm accrue, making life (and medical treatment) more problematic for patients, families, and caregivers. It is essential to minimize unpleasant experiences in order to maximize the incentive to continue necessary follow-up evaluation and management. After all, the patient is the most important member of the medical team and should be cared for as if he or she were a family member and/or a future colleague. Pain, both physical and emotional, should be carefully assessed and addressed during all phases of evaluation and intervention. Awkwardness should be mitigated, as much as possible, by the care team's dignified approach to the patient, who may potentially be embarrassed about being touched, about being different, or having a problem such as incontinence.

PREOPERATIVE EVALUATION

General Diagnostic Principles

1. Individual defects are nonspecific: diagnosis is based on overall pattern.
2. A defect may be isolated but dramatic in its presentation.
3. A defect may be isolated and seemingly minor, but have serious consequences.
4. Expression is variable.
5. Similar phenotypes may result from different etiologies.
6. The earlier the insult, the worse the outcome.
7. Minor anomalies are clues to more serious problems.
8. If there are three or more minor anomalies, evaluate for major malformation, which may be occult.
9. Recessive expression may imply lack of enzyme or metabolic product.
10. Dominant expression may imply faulty structural genes.

General Diagnostic Approach

A patient may present for evaluation for surgery and anesthesia with a urological manifestation of a known diagnosis: one can quickly use a textbook or the Internet to discover any other associated concerns for the surgeon, anesthesiologist, or pediatrician. Some conditions are so rare that discussions of anesthetic and surgical implications have not been published, especially since some conditions have allowed few survivors, but anesthesia concerns can be extrapolated and surmised from descriptions of associated problems.

Alternatively, a patient may present with an isolated routine urological problem but appear to have other anomalous features: note other abnormalities and quickly suggest a diagnosis using a textbook that groups by pattern of defects, or refer to a geneticist when appropriate. An example is a 2-year-old patient who presents for inguinal hernia repair who is noted incidentally to have axillary freckling, an abnormal finding found in several syndromes.

Families or patients may have been given a diagnosis but may not recall it. Perhaps the existence of a name

makes it worse. As time goes on, parents and patients may appreciate having the information, and anesthesiologists certainly will.

Confirming that the urological problem may be part of a larger picture may improve understanding and prediction of prognosis and care in the long term. Associated risks should be detected, such as risk of metabolic problems or latex allergy, presence or risk of renal dysfunction or failure, or presence or risk of other organ dysfunction or failure. Completing the picture may help the physicians, the family, and the patient.

Some syndromes may have other overwhelming features (craniofacial anomalies and cardiac anomalies) that distract other caregivers, patients, and families from the associated urological problems that require intervention and follow-up to prevent complications, such as renal failure.

Tables 9.1 and 9.2 are examples, not comprehensive lists, of urologic diagnoses and associations, syndromes, and sequences.

Specific Considerations

If urologic conditions may be associated with renal insufficiency, baseline renal function should be established. If the patient does have renal insufficiency, or is at risk for developing renal injury, the patient should be evaluated for electrolyte abnormalities, anemia, hypertension, and other metabolic abnormalities that may be associated with his or her overall diagnosis. If hypertension is suspected, care should be taken to measure blood pressure with an appropriate-sized cuff. Renal function and electrolytes should be followed.

Some urologic conditions, such as congenital adrenal hyperplasia, may be associated with endocrine abnormalities and may require careful management and the specific input of the patient's endocrinologist.

Children with congenital urogenital abnormalities or congenital abnormalities that lead to urological problems (neural tube defects, such as myelomeningocele) are at increased risk of developing latex allergy, and exposure should be avoided.

If neuraxial analgesia is considered, make sure the spine is normal. Alternative techniques for postoperative pain management are indicated when spinal anatomy is abnormal.

Antibacterial prophylaxis may be indicated for children with urinary obstruction, urinary infections, congenital heart disease, or other associated problems. Patients with chronic exposure to antibiotics for urological or other indications may already have developed allergies to some antibiotics. Determine what antibiotics are appropriate and order them in advance in order to allow the drug to be given in a timely manner prior to incision by the anesthesiologist. Consider baseline renal function when choosing an antibiotic and the schedule of administration.

TABLE 9.1 Urologic presentations common to multiple associations, syndromes, and sequences

Renal malformation	Genital anomalies
Frequent in	**Frequent in**
Aniridia–Wilms' tumor association Beckwith–Wiedemann syndrome Exstrophy of cloaca sequence Klippel–Feil syndrome Meningomyelocele sequence Oligohydramnios sequence Sirenomelia sequence Tuberous sclerosis VATERR association	Aarskog syndrome Aniridia–Wilms' tumor association CHARGE syndrome Exstrophy of cloaca sequence Noonan syndrome Prader–Willi syndrome
Occasional in	**Occasional in**
Aarskog syndrome Apert syndrome Beckwith–Wiedemann syndrome de Lange syndrome Down syndrome Escobar syndrome Fanconi pancytopenia syndrome Myotonic dystrophy syndrome Prader–Willi syndrome Russell–Silver syndrome Smith–Lemli–Opitz syndrome Treacher Collins syndrome Williams syndrome	Aarskog syndrome CHARGE syndrome Ehlers–Danlos syndrome Fetal hydantoin syndrome Poland sequence Proteus syndrome Russell–Silver syndrome Saethre–Chotzen syndrome Williams syndrome

The Care Team and Safe Induction of Anesthesia

Children who are not able to consent or refuse medical treatment should not be assumed to be cooperative. Safe induction of anesthesia implies not only physiological and anatomical safety, but also emotional safety. Many institutions have policies requiring or restricting parental or family presence during the induction of anesthesia or during minor procedures. We feel this should be an individual decision made considering the patient, the parents or guardians, and anyone else on the care team, including but not necessarily limited to our resident child life staff members, pediatricians, and neonatal intensive care unit (NICU) or pediatric intensive care unit (PICU) physicians, nurses, and respiratory therapists. A nonparental family member who is close to the patient and/or who is a physician might serve as a key member of the care team.

Children may also benefit from a hospital tour, even one that includes a full "rehearsal" of the events that are planned. If diagnostic studies are required prior to an operation or procedure, care should be taken to avoid incurring emotional trauma in the process. Communicate with everyone involved and coordinate the entire experience.

A child and/or a family who suffers emotional trauma while undergoing medical care may carry memories of that trauma forever, affecting all subsequent medical interactions. This affects not only the patient and family, but also subsequent medical caregivers. Avoidance of critical follow-up care is one potential result.

Thus, induction of anesthesia should be planned carefully, with the patient and other involved parties, considering the patient and any past experiences with medical care

TABLE 9.2 Examples of urologic problems, associations, and etiologies

Diagnosis	Urologic	Associated	Mechanism
Aarskog syndrome	Shawl scrotum, phimosis, cryptorchidism, inguinal hernias	Hypertelorism, brachydactyly, short stature, pleasant personality, attention deficit disorder, slightly lower IQ, widow's peak, abnormal teeth, short neck, spina bifida occulta, vertebral abnormalities	X-linked recessive, gene codes for Rho/Rac guanine nucleotide exchange factor, involved in growth regulation and signal transduction
Aniridia–Wilms' tumor association (WAGR syndrome)	Present with hypospadias or cryptorchidism	Moderate to severe mental retardation, prominent lips, micrognathia, ears aniridia ptosis, cataract growth deficiency, microcephaly; look for Wilms' tumor, 1:70 with aniridia	Caused by chromosomal deletion
Apert syndrome	Present with (10%) polycystic kidney hydronephrosis, cryptorchidism, bicornuate uterus, vaginal atresia	Irregular craniosynostosis, midface hypoplasia, syndactyly, broad thumbs, great toes	Autosomal dominant, sporadic, older paternal age: mutations in fibroblast growth factor receptor 2 gene chromosome 10
CHARGE association	Genital hypoplasia in males (75%)	Colobomatous malformation sequence (80%), atresia choanae (58%), growth deficiency, postnatal (87%), mental deficiency (94%), ear anomalies (88%)	Etiology unknown
Exstrophy of bladder sequence	Exstrophy of bladder		Failure of infraumbilical mesenchyme to intercede between bladder portion of cloaca and overlying ectoderm, allowing cloacal membrane to break down, exposing posterior bladder wall (1:30,000, M > F)
Fetal hydantoin syndrome	Renal malformation, hernias, hypospadias, micropenis, ambiguous genitalia cryptorchidism	Growth deficiency, craniofacial abnormalities, hypoplastic phalanges, short neck, rib anomalies, hirsutism, brain anomalies, cardiac anomalies	Dilantin or one of its metabolites; also other anticonvulsants
Russell–Silver syndrome	Posterior urethral valves, hypospadias, renal anomalies, testicular seminoma, Wilms' tumor	Prenatal onset of short stature, skeletal asymmetry, small incurved fifth finger, small triangular facies, small chin, café au lait spots, normal head circumference, sweating and hypoglycemia in infancy, small proportionate adult with normal intelligence (often assumed to be younger than they are); treat with dignity	Etiology unknown, sporadic
Treacher Collins syndrome	Cryptorchidism	Malar hypoplasia, downslanting, palpebral fissures, lower lid defect, ear malformation, cleft palate, scalp hair on lateral cheek, cardiac defects, choanal atresia	Autosomal dominant, 60% fresh mutations, variable, chromosome 5
Urethral stricture	Urethral stricture		Acute or chronic trauma, some unexplained
VATERR association	Renal anomaly (53%)	Vertebral anomalies (70%), ventricular septal defect and other cardiac defects (53%), anal atresia ± fistula (80%), radial dysplasia (65%), single umbilical artery (35%)	Etiology unknown
von Hippel–Lindau syndrome	Renal cysts, pheochromocytoma, renal cell carcinoma, hypernephromata, epididymal cysts	Angiomatous tumor of the central nervous system; hemangiomas of face, adrenal, or lung; liver cysts; cancer of pancreas; cancer of ampulla of Vater; paragangliomas; polycythemia	May have only one lesion, many cases unrecognized, autosomal dominant with variable expression, chromosome 3, altered tumor suppressor gene

or anesthesia. A child's requests, if any, should be honored, if possible, and options, if safe, should be entertained.

Anxiolytics (midazolam) prior to entering the operating room (OR) are fairly routine for children once they begin to experience anxiety with separation from parents. However, some children who undergo repeated procedures grow to dislike the taste of the drug given orally or the symptoms of the drug. Some dislike the taste (even when preflavored) so much that they reflexively wretch; others have been traumatized by the discomfort of nasal administration or the memory of an intramuscular (IM) injection.

Even young patients may request no midazolam, and their requests should be considered.

Parental Absence

Options are whether to take midazolam or whether to have a parent present for induction—neither or either or both. A child life therapist with an exciting iPad app might be more effective than medication for some children. Choices should be offered where they exist, but it should clearly be stated when there are no further options, rather than withholding this truth from a child.

Parental Presence

A 2-year-old patient from the burn unit came down with her mother to the OR for a minor procedure. She had an IV and so was given 0.5 mg IV of midazolam. This had no effect. She continued to cling to her mother and would let no one else near her. More midazolam, up to 2 mg, plus fentanyl, was given, to no significant effect. The anesthesiologist whispered to the nurse, "The bunny suit." The mother was quickly outfitted in a paper coverall, hat, and mask, and assisted into the gurney on her left side with her toddler curled in her arms. The team studiously ignored the mother and child as they were wheeled quietly into the OR. The gurney was parked parallel to the OR table with the child closest to the anesthesiologist who was stationed between the gurney and table, with her head nearest the foot of the table. The pulse oximeter probe and the mask were ready but not yet on the patient. A dose of propofol insufficient to cause apnea was administered. As the child began to relax, the anesthesiologist scooped up the child and spun around, depositing the child on the table as the mother and gurney were quickly wheeled from the room.

INTRAOPERATIVE MANAGEMENT

Safe Airway Management

The position of the patient and where he or she is placed on the table, as well as the length of the case and the need for neuromuscular blockade, will determine, in part, the mode of airway management. A cystoscopy, which might otherwise be brief enough to allow airway management by mask alone, would require at least a laryngeal mask airway (LMA) because the patient must be positioned at the extreme foot of the table. Very small patients can lie across the bed, allowing access to the airway, and may not require more than a mask for a brief cystoscopy.

Another consideration is whether the patient has craniofacial or airway anomalies, making airway management more challenging. A child is not expected to cooperate with awake intubation, and pediatric anesthesiologists have devised methods of managing even the difficult pediatric airway without having to struggle with an awake and uncooperative child.

Vascular Access, Invasive Monitoring, and Fluids

Large operations involving blood loss and fluid shifts may necessitate placement of an arterial line or central line, especially if the child has had a significant number of prior operations, potentially making blood loss more likely and limiting peripheral IV access, and/or the recovery period will be critical or prolonged. It is helpful to anticipate this need and to plan and schedule accordingly.

The use of irrigation or surgical interruption of the urogenital system may make it impossible to utilize urine output to monitor fluid status. The use of irrigation fluid increases the risk of hypothermia via cooling of a body cavity or because the surface on which the body rests becomes damp or saturated. Use warmed irrigation fluid and apply clear plastic sticky drapes at the perimeter of the surgical field before prep to direct fluid, even warmed fluid, which will inevitably cool, away from the body.

Irrigation fluid also makes estimation of blood loss problematic. The amount of irrigation fluid used should be tabulated in order to subtract it from the total volume in the suction container. Large suction systems make estimating blood loss difficult, especially in smaller patients. If there is concern about the potential for blood loss or a patient develops hemodynamic instability possibly attributable to blood loss, and there is no arterial line, hemoglobin may be measured with a small amount of blood from a finger stick or estimated using a noninvasive hemoglobin monitor.

The use of diuretics in certain procedures may also contribute to uncertainty about fluid status, making communication and careful assessment of irrigation, blood loss, fluids administered, insensible fluid losses, and if possible, urine output even more essential.

Medication for Sedation and Anxiolysis

The recommended dose for oral midazolam for sedation and amnesic purposes preoperatively is 0.5–0.7 mg/kg. Children with autism may require doses closer to 1 mg/kg. Many anesthesiologists do not exceed a total dose of 12–20 mg orally. The drug comes premixed with syrup in a 2 mg/mL concentration for oral administration. The 5 mg/mL concentration can also be mixed with syrup. Younger children may be used to taking medication via a syringe; older children may accept the challenge of squirting the syringe quickly by themselves.

When intranasal (IN) midazolam must be given, the dose is 0.3 mg/kg of the 5 mg/mL concentration. This route should only be used in the patient if no other method will be effective, since patients will recall the burning sensation it causes. However, absorption is rapid.

When a larger child is unable to cooperate with either IV placement or induction, IM sedation may be the best choice before induction. Midazolam dose ranges from 0.1 to 0.15 to 0.5 mg/kg, and midazolam may be mixed in the same syringe with a ketamine dose of 1, 2, or 5 mg/kg (with 0.02 mg/kg atropine to prevent hypersalivation caused by ketamine).

If the patient already has an IV, the initial dose for IV midazolam is 0.05–0.1 mg/kg for patients 6 months through 5 years of age, although a total dose of up to 0.6 mg/kg may be necessary in patients who are not naïve to midazolam, and 0.025–0.05 mg/kg for patients 6–12 years of age, although a total dose of up to 0.4 mg/kg may be necessary in patients who are not naïve to midazolam. Patients over 12 years of age should be dosed as adults, with 1–2 mg midazolam.

Choice of Anesthetic Agents

The cooperation of a child should not be taken for granted; thus, general anesthesia should be assumed. The question of whether to place a preinduction IV, if one is not already in place, should be somewhat dependent on the child. A young child with little exposure to anesthesia might find an IV far more threatening than an inhalation induction, but a child with repeated exposures may prefer IV placement over inhalation. Sevoflurane is the least noxious of the volatile anesthetics in use today and is the only volatile agent of choice for induction (halothane is now rarely used). The volatile agents with more noxious odors, isoflurane and especially desflurane, may provoke struggling, salivation, coughing, and laryngospasm, with disastrous results. Nitrous oxide mixed with oxygen is employed briefly at the beginning of induction to provide some sedation before sevoflurane is introduced slowly into the anesthesia circuit to accelerate the speed of induction. In some cases, a rapid induction is achieved by prefilling the circuit with oxygen, nitrous oxide, and 8% sevoflurane. The volatile agent causes peripheral vasodilatation, making it somewhat easier to start an IV, but caution needs to be taken when inducing a child who is hypovolemic or has congenital cardiac anomalies. A high dose of sevoflurane can lead to severe hypotension, bradycardia, and even cardiac arrest during induction. Peripheral dilatation also leads to heat loss—thus the necessity for hot-air warming devices, as well as warmer rooms for smaller patients.

The very youngest patients, those from the NICU, may not tolerate volatile anesthetics, and may instead require high doses of opioids, usually fentanyl, as their agent of choice for general anesthesia. These patients are usually not extubated immediately postoperatively.

Positioning

Positioning requires careful attention, especially in long cases. The head and neck should be in a neutral position, and limbs should be slightly flexed and adducted rather than extended and abducted, in order to prevent traction on tendons and nerves, especially in the high lithotomy position. Arms should be positioned level with or anterior to the midline in the coronal plane to avoid stretching the brachial plexus. In obese patients, who carry an extra-thick "mattress" on their backs, this can be accomplished only by placing extra padding on the arm boards, if utilized, to raise the level of the arms. If arm boards are used, and the table position is other than level, the arms should be secured to keep them from falling off under the drapes. Padding should be used appropriately to prevent pressure injuries. Especially during long cases, the head and limbs not in the surgical field should be moved or repositioned subtly and on a regular basis to avoid prolonged pressure on any single surface, such as the back of the head, or postoperative soreness from maintaining a single position. If the prone position is necessary, care must be taken to avoid pressure on facial structures or the anterior surface of the body. The airway device should be protected, and care should be taken not to rest instruments or hands on the face or to compress the chest. This can be especially challenging in smaller patients.

Antiemetics

While not given routinely in infants and small children, antiemetics may be required in patients who exhibit postoperative nausea and vomiting (PONV). Ondansetron, droperidol, and metoclopromide are and have been used frequently in pediatric patients, although there are many other antiemetics. Ondansetron, one of the most commonly used antiemetics, is a serotonin 5-HT_3 receptor antagonist that affects both peripheral and central nerves, reducing vagal nerve activity, deactivating the vomiting center in the medulla oblongata, and blocking serotonin receptors in the chemoreceptor trigger zone. Other drugs in this class include granisetron, dolasetron, and tropisetron. The clinical effect of drugs of this class can be potentiated by dexamethasone.

Metoclopromide is a nonselective 5-HT_3 receptor agonist.

Droperidol is a butyrophenone and is a D_2 dopamine receptor antagonist with a central antiemetic action. Its antiemetic effect lasts much longer than its sedative effect, so when used, it is given very early in the anesthetic, unlike ondansetron, which must be given close to emergence from anesthesia.

Antiemetic Dosing

Drug	Age/Weight	Dose
Ondansetron IV	1 months–12 years; 40 kg or less	0.1 mg/kg
	>12 years; 40 kg or more	4 mg
Ondansetron ODT oral disintegrating tablet, for nausea and vomiting and no IV	4–11 years; 40 kg or less	4 mg
	>11 years; 40 kg or more	8 mg
Droperidol IV		10 μg/kg every 6 hours
Metoclopromide IV	>14 years	10 mg
	6–14 years	2.5–5 mg
	<6 years	0.1 mg/kg

Principles of Dosing Enteral and Parenteral Drugs

Consider the developmental stage, the weight and body habitus, the history of pain medication use, the degree of tissue damage sustained during the course of the operation, and the setting in which pain medications are prescribed.

Weight might not be proportional to height or length or developmental or chronological age; disproportionate weight can actually reflect a medical or social problem.

All pediatric drug orders and prescriptions should include weight, and for patients well outside the normal in terms of body mass index (BMI), one should consider including BMI as well.

Ideal body weight or lean body weight should be calculated and considered when weight is out of proportion to height and age.

Dosing for pediatric patients who weigh less than 50 kg is in milligrams or micrograms per kilogram.

Dosing for pediatric patients who weigh equal to or more than 50 kg is similar to adult dosing, if BMI is normal.

Calculating a Pediatric Dose Using Ratios

- Dosing for pediatric patients in the 50–70 kg range can be better determined by using a ratio to determine the dose per kilogram: 1/70 kg × Adult dose (in units/kg) = Dose in units/kg.
- Thus, for an acetaminophen dose of 1000 mg every 6 hours for an adult, 1/70 × 1000 mg = 14.3 mg/kg and 14.3 mg/kg × 55 kg, and so, more conservatively, a 786 mg acetaminophen dose would be for a 55 kg patient.

Older children and adolescents who are developmentally appropriate can tolerate patient-controlled analgesia (PCA), but PCA by proxy for younger children is not recommended, with exceptions. Some parents become very experienced in helping to manage their child's pain.

Drugs should be "layered" as pain management is escalated, starting with nonopiates, such as local anesthetics (a temporary solution for immediately postoperatively), acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs) (if not contraindicated), and sometimes gabapentin, if a patient can tolerate oral medication. These drugs should be continued even when opiates and ketamine are added during necessary escalation of pain management.

Assessing Pain in Children

Evaluation of pain in children is problematic, especially when children are not able to use words.

Infants have no verbal skills and are entirely dependent on the clinician or parent for pain assessment. Signs of pain may include disturbances in eating and/or sleeping; rigid posture, including bringing the knees up to the chest; crying and other vocalizations signaling distress; and facial expressions.

Toddlers may have minimal vocal skills. Even when they are able to report the presence of pain, they are unable to describe it (this may persist into adult life in some people). They are vulnerable to secondary gains (attention, treats, and new toys). They also have trouble understanding cause and effect. Toddlers may also exhibit, as signs of pain, disturbances in eating and/or sleeping, guarding or thrashing about, crying and other vocalizations signaling distress, regression to more immature behavior, and clinginess to parent or other caregiver. Facial expressions may also give evidence of pain.

School-aged children are able to verbalize pain and can be more descriptive. They may also be vulnerable to secondary gains (watching television, missing school, treats, and gifts) and may exaggerate their pain. They may exhibit as signs of pain, stiffness, or rigidity, as well as eating or sleep disturbances. Facial expressions are also a key to the level of pain.

Pain assessment is thus age dependent, but the patient should be questioned to the limit of his or her ability to respond. A pain rating scale, using either faces or numbers, can be utilized. Observe behavior and physiological signs. Enlist the family and listen to their assessment, since they know their child's baseline. Consider the cause of the pain. Treat and continue to assess the effectiveness of the treatment.

PAIN MANAGEMENT

Escalating Pain Management

1. Local anesthetics and nonopioid adjuvants include aspirin, acetaminophen, NSAID, gabapentin, and clonidine.
2. Add an opioid for mild to moderate pain: codeine (if effective) or hydrocodone (*stop* plain acetaminophen, aspirin, or NSAID if prescribing combination drugs).
3. Add an opioid for moderate to severe pain: morphine, oxycodone, hydrocodone, fentanyl, methadone, or ketamine.

Use noncombination drugs in order to prevent confusion leading to acetaminophen toxicity. If using a combination drug, make it very clear that either acetaminophen *or* the combination drug may be used.

Start with low doses and titrate upward, but be aggressive about managing pain.

Medication for Pain Management

Opioids

Opioids are central-acting analgesics used to treat moderate to severe pain. Administration can be oral, nasal (given as a small dose just prior to the end of a short outpatient procedure to treat immediate pain and ease emergence from anesthesia), parenteral, neuraxial (spinal or epidural), or transdermal (fentanyl patch, usually prescribed for palliative pain). Parenteral opiates are usually prescribed for acute moderate to severe postoperative pain. Oral opioids are available as elixirs or pills or tablets, and as single drugs or in combination with acetaminophen, aspirin, or NSAIDs, and are usually prescribed for acute mild to moderate postoperative pain or as soon as a patient is able to tolerate oral medication.

Morphine, a natural derivative of opium, has been in use for more than 150 years. Substituted semisynthetic

(oxycodone and hydrocodone) and complex synthetic (meperidine, fentanyl, and methadone) opioids are widely used to treat moderate to severe pain.

Morphine, which has a half-life of 3 hours, is the basic unit of comparison with other opioids; 1 mg of morphine is equivalent to 0.2 mg of hydromorphone, 50 μg of fentanyl, and 10 mg of meperidine.

Opioids bind to binding sites for endogenous substances, such as endorphins and enkephalins, which modulate the transmission and perception of pain because they are structurally and chemically similar. Although opioids reduce or eliminate the suffering from pain, they do not, unlike local anesthetics, ablate the perceived location of the pain. Unlike local anesthetics, they do not affect the sensation of light touch, pressure, and temperature.

Four Opioid Receptor Subtypes

- Mu, or opioid receptor subtype 1, mediates supraspinal analgesia, respiratory depression, nausea and vomiting, miosis, bowel hypermotility, euphoria, physical and psychological dependence, and increased release of prolactin and growth hormone. Mu receptors are widely studied.
- Kappa, or opioid receptor subtype 2, mediates spinal and visceral analgesia, as well as sedation, but seems not to have much of an effect on respiration. There are peripheral kappa receptors found in the gastrointestinal tract, skin, muscle, and connective tissue, providing analgesic, antineuropathic, and anti-inflammatory effects. Kappa receptors in the kidney are associated with antidiuresis and oliguria.
- Delta, or opioid receptor subtype 3, seems to enhance, facilitate, or modulate the effects of mu and kappa receptors.
- Sigma-1 receptors, no longer considered true opioid receptors because they are not affected by opioid antagonists, are believed to mediate opioid-associated dysphoria, hallucinations, and confusion.

It was long assumed that individual responses to opioids were similar. However, opioid receptor pharmacogenomic research has revealed genetic variants in receptors and other genes involved in responses to opioids. Patients differ in their responses to different opiates. While it is presently impractical to pretest patients in order to prescribe opiates effectively, it becomes evident which drugs are effective in a given patient.

While patients should be on a regular pain regimen, doses for breakthrough pain should always be available.

Drug doses for the treatment of opioid side effects should be calculated in advance.

Listen to the patient and their families when they describe side effects and intolerance associated with specific opioids and not with others. Many times, physicians erroneously interpret this behavior as "drug seeking." These patients and families have observed the effects of their genetic uniqueness in their responses to given drugs. Some drugs do cause dysphoria, hallucinations, or severe itching and may not treat pain effectively in given patients. An overly sedated patient can still be in pain but be unable to communicate this.

Parenteral Opioids

Parenteral Opioid Doses

Drug	Dose <50 kg	Dose >50 kg
Morphine	Bolus 0.1–0.3 mg/kg every 2–4 hours	Bolus 5–8 mg every 2–4 hours
	Infusion 0.2–0.3 mg/kg/hour	Infusion 1.5 mg/hour
Fentanyl	Bolus 0.5–1.0 μg/kg every 1–2 hours	Bolus 25–50 μg every 1–2 hours
	Infusion 0.5–2.0 μg/kg/hour	Infusion 25–100 μg/hour
Hydromorphone	Bolus 0.01–0.02 mg/kg every 2–4 hours	Bolus 1 mg every 2–4 hours
	Infusion 0.006 mg/kg/hour	Infusion 0.3 mg/hour

Patient-Controlled Analgesia

Components of a PCA include drug choice (usually morphine, fentanyl, or hydromorphone), loading dose, PCA bolus dose, basal rate (if any), lockout time, and maximum hourly dose.

Morphine is often the default drug for PCA. The loading dose should average about 100 μg/kg. The bolus dose should start at 0.03 mg/kg. The basal rate (if any) should average about 0.03 mg/kg/hour, with a 6- to 10-minute lockout time. The maximum hourly dose should be about 20 μg/kg. If pain is not controlled, the bolus dose should be increased by 10%–20%. Other maneuvers are to increase the basal rate infusion (if any) by 20%–40%, decrease the lockout time, and make sure the patient is not consistently reaching the hourly maximum dose. It may be necessary to switch to another opioid if morphine is ineffective.

If the patient is experiencing side effects, treat the treatable side effects individually (itching, nausea and vomiting, and constipation) or switch opioids, often necessary when side effects include hallucinations or dysphoria.

Oral Opioids

For children too young to swallow pills, but who are able to swallow a liquid, an elixir is an excellent choice, although not all pharmacies can supply liquid opiates. Options are morphine regular release in various concentrations, hydromorphone, codeine alone and in combination with acetaminophen in various strengths (the dose of acetaminophen stays the same), hydrocodone in combination with acetaminophen, methadone, oxycodone, and oxycodone in combination with acetaminophen. When pain is expected to be somewhat short term, oxycodone can be given around the clock. When pain is expected to be more long term, oxycodone HCl CR (OxyContin) or MS Contin can be prescribed. Older children, who are able to swallow pills, can be prescribed opioids in tablet form.

Drug	Dose <50 kg	Dose >50 kg
Codeine	0.5–1 mg/kg every 3–4 hours	30–60 mg every 3–4 hours
Morphine	Immediate release	Immediate release
	0.3 mg/kg every 3–4 hours	15–30 mg every 3–4 hours
		Sustained release
		30–45 mg every 3–4 hours
Oxycodone	0.1–0.2 mg/kg every 3–4 hours	5–10 mg every 3–4 hours
Methadone	0.1 mg/kg every 4–8 hours	10 mg every 4–8 hours
Hydromorphone	0.04–0.08 mg every 3–4 hours	2–4 mg every 3–4 hours

Oral Opioid Doses

Codeine is a weak opiate with many side effects, including nausea and vomiting, and is not considered a first-line treatment for pediatric patients. Codeine becomes effective after being metabolized to its active metabolite morphine by cytochrome P-450 in the liver. Many people (including people of Asian, Arab, and African American descent) are unable to metabolize codeine; thus, they cannot benefit from the drug. On the other hand, 0.5%–2% of patients are extensive metabolizers, which can lead to a more pronounced than expected effect from codeine, potentially leading to overdose. On August 15, 2012, the Food and Drug Administration (FDA) warned physicians and caregivers about the risks of giving codeine to children, especially those with sleep apnea, because of the variable rate in which individuals metabolize codeine, placing some children at risk of overdose. A further bulletin was released by the FDA on February 20, 2013.

Transitioning from Parenteral to Oral Opioids

When a patient who has been on parenteral opioids needs to be transitioned to an oral equivalent, an equianalgesic oral dose of the drug that has been effective for the patient should be determined, as a starting dose. When it is necessary to switch drugs, as would be the case for a patient who was on fentanyl, use an IV dose of the new drug equivalent to that of the previous drug (Table 9.3), and use the parenteral–oral ratio to determine the dose of the oral drug. Thus, 100 μg IV of fentanyl is equivalent to 2 mg IV of morphine, so an oral dose of morphine would be 6 mg.

Acetaminophen

Acetaminophen is the most commonly prescribed nonopioid analgesic. The mechanism of action is the central inhibition of cyclooxygenase. The drug causes no adverse effects on gastrointestinal motility, renal function, or platelet function. It is available for oral, rectal, and IV administration.

Doses for neonates and infants are best determined by a pediatric specialist. However, children over 6 months to 2 years can tolerate a rectal dose of 90–120 mg/24 hours, divided to allow q4–q6 hour dosing intervals or an oral dose of 90 mg/kg/day, again divided to allow q4–q6 hour dosing intervals.

Children 2–12 years can tolerate a rectal loading dose of 40 mg/kg, followed by rectal doses of 20 mg/kg every 6 hours. Oral doses in this age group are 10–15 mg/kg every 6 hours.

The IV dose for children of 2–12 years and <50 kg who are unable to take either oral or rectal acetaminophen, given as an infusion over 15 minutes, is 15 mg/kg every 6 hours, with a maximum dose of 75 mg/kg/24 hours. For children of >50 kg, the dose is 1000 mg every 6 hours, given as an infusion over 15 minutes, with a maximum dose of 1000 mg/24 hours. In the 50–65 kg range, however, consider continuing weight-based dosing, which gives a lower dose.

Nonsteroidal Anti-Inflammatory Drugs

The mechanism of action of NSAIDs involves the inhibition of cyclooxygenase in the periphery. NSAIDs are a useful adjunct to opioid therapy in the acute pain setting, when not contraindicated by unacceptable side effects. Prolonged use is not recommended.

Ibuprofen is the most commonly used oral NSAID for outpatient pediatric pain relief, and it can be used in alternating fashion, every 6 hours, with acetaminophen *or* a combination oral drug containing acetaminophen and an opioid, such that the patient receives one drug every 3 hours, immediately postoperatively. The dose is 10 mg/kg in patients ages 2–12 who are <50 kg.

As pain diminishes, the ibuprofen should be discontinued first, followed by the opioid, in favor of plain acetaminophen as necessary.

Ketorolac may be given, if desired, as one IV dose immediately postoperatively, at a dose of 0.5 mg/kg, with a maximum dose of 15–30 mg.

TABLE 9.3 Parenteral to oral

Drug	Parenteral dose	Oral dose	Parenteral: Oral ratio
Morphine	10 mg	30 mg (long term)	1:3
Fentanyl	100 μg	No oral equivalent	N/A
Hydromorphone	1.5–2 mg	6–8 mg	1:4
Methadone	10 mg	10–20 mg	1:2

Abbreviation: N/A, not applicable.

Adjunct Pain Medications

Adjunct pain medications include gabapentin (40 mg/kg/day given in divided doses three times per day), indicated when pain is more chronic in nature. Ketamine has been used in chronic pain management, especially in patients who are tolerant to opioids, but should be prescribed, after evaluation, by a specialist in pediatric pain management.

Local Anesthetic Agents

The mechanism of action of local anesthetics is reversible inhibition of the conduction of neural impulses along central and peripheral nerve pathways. To be effective, local anesthetics must be manually deposited in the immediate vicinity of the nerves to be blocked, and therefore are virtually unlike any other class of anesthetic or analgesic medication. Duration of action is determined by washout by local blood supply, resulting in spontaneous recovery of nerve function without evidence of any structural detriment to the nerve tissue.

For decades, children were considered poor candidates for local anesthetic techniques not only because of their fear and distress of needles, but also because of the resultant pain caused after injection of local anesthesia. Children were thus unable to benefit from regional anesthetic techniques in the management of procedural and postprocedural pain. There was the added assumption that children did not "feel pain," which is evidenced by the fact that until 1980, children were not given intraoperative opioids and were given very little anesthetic for surgery. Local anesthesia can provide complete anesthesia in situations where general anesthesia is neither practical nor possible, such as in newborn circumcision and management of postprocedural pain.

In brief, local anesthetics inhibit sodium (Na+) conductance during an action potential. During an action potential, voltage-gated Na+ channels open briefly, allowing extracellular Na+ to enter the cell. This phenomenon is called depolarization of the plasma membrane. Local anesthetic molecules block neural conductance in peripheral, spinal, and cortical axons by inhibiting Na+ from entering or by interfering with conformational changes that allow the channel to depolarize. Again, local anesthetics do not alter the resting potential of the membrane; they block sodium permeability at specific ion-gated sodium channels and *slow* the rate of depolarization so that an action potential is inhibited.

The minimal concentration of local anesthetic necessary to block impulse conduction along a given nerve is called the Cm. Factors that affect the Cm include fiber size, myelination of nerve, pH, local calcium concentration, and the rate at which an action potential along a given nerve is transmitted. Each local anesthetic has a unique Cm, which reflects the differing potencies of each drug. For example, unmyelinated fibers (C and Ad) have a lower Cm than heavily myelinated fibers (AB). Because of the lower Cm, less local anesthetic is needed in dose and volume to block nociceptive transmission than to block muscle contraction or motor conduction.

The choice of which local anesthetic agent is suitable depends on multiple factors, primarily the type of blockade needed (analgesia vs. anesthesia), route administered (subcutaneous, peripheral nerve block, epidural or caudal, or spinal), onset time, duration of action, and presence of patient comorbidities (i.e., decreased hepatic function). Where and *how* neural block is performed determines the decision concerning which local anesthetic to use. For example, some local anesthetics cannot be used intrathecally (chloroprocaine). Otherwise, in most clinical situations, the choice of local anesthetic is determined by duration of action, and very infrequently by onset of action, as long-term postoperative analgesia is the ultimate goal.

Types of Local Anesthetics

Local anesthetics all contain a lipophilic aromatic ring, a hydrophilic tertiary amine, and an ester or amide linkage between the aromatic ring and the tertiary amine. Thus, local anesthetics are all classified as either "amide" or "ester" based on the type of linkage. All amide local anesthetic names contain the letter i in the first part of the word (excluding the "caine," which all share).

Amides and Esters

Amides	Prilocaine Lidocaine Ropivacaine Bupivacaine Levobupivacaine
Esters	Tetracaine Benzocaine Cetacaine

Chemical groups attached to the aromatic ring have an influence on the speed of onset, while groups attached to the tertiary amine have an influence on anesthetic potency and lipid or aqueous solubility. Epinephrine mixed with local anesthetic (lidocaine and bupivacaine), when not contraindicated, prolongs duration by vasoconstriction and decreased blood flow.

Typical Applications of Local Anesthetics

Topical Tetracaine can be used on the eye. Cetacaine can be used on nasal, oral, and laryngeal mucosa. Prilocaine can be used on the skin, whether intact or damaged. Lidocaine can be used in the urethra.	**Neuraxial** Bupivacaine can be used for intrathecal, caudal, or epidural (single shot or continuous). Tetracaine can be used for spinal. Lidocaine can be used for epidural. Ropivacaine can be used for caudal or epidural. Levobupivacaine can be used for caudal or epidural.
Infiltration Lidocaine, ropivacaine, bupivacaine, and levobupivacaine can all be used for field blocks or specific nerve blocks (brachial plexus, ankle, intrabulbar, retrobulbar, dental, etc.).	**Miscellaneous** Bupivacaine can be used for trigger point injections. Lidocaine alone can be used for IV regional (Bier) block; it is also used to treat chronic regional pain syndrome.

Regional and Neuraxial Techniques

Generally, regional anesthesia is used when systemic therapeutics are expected to or have failed to provide adequate analgesia, or when adverse effects from opioids are excessive, or when the initial surgical or postsurgical insult will be too great and there is anticipation that IV or enteral routes of administration of analgesics will be ineffective. Advantages also include possible blockade of transition from acute pain to chronic, persistent pain states in children, in which the pain has considerable adverse influence on the child's daily functions and prevents the child from participating in his or her normal roles, irrespective of the child's coping ability.

In the past, the main challenge was in identification of pain, and adequate pain assessment in neonates, infants, and small children. Over time, the issue has advanced to which pharmacologic agents would be appropriate for this age group, at which dose, and how to minimize toxicity. Expectations from parents have also evolved; a high degree of comfort and pain relief is now expected. All attempts are made to apply best evidence-based clinical practices to the use of regional and neuraxial anesthesia and analgesia in children; however, there are often no prospective, randomized double-blinded controlled trials of regional anesthesia in the pediatric population. As a result, most data that guide therapy are extrapolations from the adult literature, where possible.

The basic requisites for safe and effective regional and neuraxial anesthesia include selection of the best strategies for postoperative analgesia. This begins with an evaluation for expected anatomical location of pain, duration of analgesia required, expected intensity of postoperative pain, and surgical technique. Within these contexts, there is considerable influence on the anesthesiologist's decision regarding type of regional blockade.

In most surgical procedures, a single-shot nerve block (whether peripheral or caudal) is appropriate in terms of duration of anesthesia and associated morbidity outcomes. Moreover, most single-shot nerve blocks are appropriate for outpatient surgical procedures. As a general rule, motor block is generally very poorly tolerated by neonates and infants and should be avoided when at all possible. Discharge from the recovery room is generally not precluded by persistent sensory block; however, motor block may delay discharge in order to monitor for compartment syndrome. If motor block is suspected, likely culprits include postlumbar plexus block or ilioinguinal nerve block performed where the motor branch of the femoral nerve may be blocked. If long-lasting analgesia is required, particularly after extensive surgical reconstruction, a postsurgical epidural or caudal catheter can be placed for infusion of continuous local anesthetic and/or opioids. Ideally, since the child is still under general anesthesia during the placement of the neuraxial block, signs and symptoms of local anesthetic toxicity or total spinal anesthesia may be masked, and therefore a greater margin of safety is required for placement. In these scenarios, placement with fluoroscopic guidance, nerve stimulation-guided technique, or ultrasound guidance technique is highly recommended to guide visualization of the needle and minimize complications of the regional block, as well as in those patients at risk for compartment syndrome (i.e., those who will require plaster casts postoperatively).

The caudal block is one of the most frequently applied techniques to access the epidural space in pediatric patients. It is particularly useful for achieving excellent sensory analgesia after urological procedures, and can be used as the sole anesthetic when required. Briefly, the patient can be positioned in the prone or in the lateral decubitus position. The border of the caudal canal is the line intersecting the two sacral cornua superiorly and the sacral hiatus inferiorly (triangle formation). The needle is inserted at the top of the gluteal fold in the sacral hiatus and advanced until the sacrococcygeal ligament is punctured. A loss of resistance will be noted, suggesting puncturing of the sacrococcygeal ligament. Once through the ligament, the needle is then flattened and advanced 1–2 mm. Local anesthetic is then deposited after confirmed negative aspiration for heme or cerebrospinal fluid (CSF) and after a negative test dose.

COMPLICATIONS OF ANESTHESIA AND PAIN MANAGEMENT

Side Effects and Complications of Opioids

Continued exposure to opioids leads to the development of tolerance and physical dependence or addiction.

Tolerance is the progressive increase in dose required to maintain the same desired pharmacological effect.

Physical dependence is normal and commonly observed in opioid-tolerant patients. Parasympathetic tone is increased when opioids are discontinued abruptly and patients experience symptoms of withdrawal: sweating, shaking, cramping, and diarrhea.

Psychological dependence includes drug-seeking behavior and use of drugs for purposes other than pain control.

While patients suffering moderate to severe acute pain may experience physical dependence on opioids, they do not often experience psychological dependence.

Addiction is the term used to describe an extreme form of psychological dependence where patients experience craving and impaired control with compulsive use despite incurring harm. This behavior is reinforced by physical dependence and fear of withdrawal.

Opioid-induced hyperalgesia (OIH) occurs in patients who have developed tolerance to opioids, but has been observed in patients newly exposed to rapid-acting short-duration opioids, such as remifentanil and alfentanil. OIH is characterized by hyperesthesia (paradoxical increases in the intensity of pain), allodynia (changes in the characteristics of the pain), and new pain complaints in response to continuous administration or increased dosing of opioid analgesics.

Other undesirable side effects include respiratory depression, bradycardia, constipation, urinary retention, pruritis, oversedation, hallucinations, delirium, and nausea and vomiting.

Narcotic Antagonists

Naloxone is used to treat opioid-related respiratory depression. The standard dose is 10 μg/kg IV push every 3 minutes

in patients of <40 kg. However, this dose, equivalent to the standard adult dose of 0.4 mg or 400 μg, should not necessarily be given at once unless the situation is dire and opioid overdose is massive. In the case of massive overdose, with apnea, naloxone up to 50–100 μg/kg can be given to patients of <40 kg and up to 2–4 mg in patients of 40 kg or greater. Doses of this magnitude are rarely required.

Positive pressure ventilation should be initiated immediately, after which 1–2 μg/kg IV push should be given, and then repeated every 3 minutes. A patient of <40 kg who requires more than 2 μg/kg or a patient of 40 kg or greater who requires more than 0.08 mg or 80 μg will really need to be intubated and remain intubated until the excess narcotic, which has a longer half-life than naloxone, wears off, in order to avoid another event.

Diphenhydramine is used to treat opioid-associated pruritis. The standard dose is 5 mg/kg/24 hours, given every 6–8 hours—thus 1.25 mg/kg every 6 hours or 1.67 mg/kg every 8 hours in patients of >1 year of age.

Stool softeners are recommended to prevent and treat opioid-related constipation.

Acetaminophen Toxicity

Metabolism of acetaminophen is hepatic, via three pathways: conjugation with sulfate, conjugation with glucuronide, or metabolism via the cytochrome P-450 oxidase enzyme system. Ninety percent of the metabolism of an ingested dose is by conjugation, but the approximately 5% via the P-450 system produces N-acetyl-p-benzoquinone imine (NAPQI), which is directly hepatotoxic. Reduced glutathione, an antioxidant compound in the liver, renders NAPQI harmless, and NAPQI-reduced glutathione is then excreted by the kidneys.

In the case of acute or chronic acetaminophen overdose, the sulfation and glucuronidation pathways become saturated and the amount and rate of formation of NAPQI are greatly increased, depleting reduced glutathione stores, allowing NAPQI to bind to hepatocytes, causing cell death.

Symptoms are nonspecific, and include nausea and vomiting. Laboratory evidence of liver damage will not be immediately evident. Elevated serum levels of acetaminophen can predict toxicity, however, if the timing of acute ingestion is known, but are not predictive after chronic, repeated ingestion.

The antidote for acetaminophen poisoning is N-acetylcysteine, which works to prevent or limit liver damage if toxicity is detected and treated in time.

Side Effects and Complications of NSAIDs

Side effects and complications include coagulopathy, gastrointestinal bleeding, bruising, bleeding at the site of the wound, renal injury, bronchospasm, and bone marrow suppression. NSAIDs should not be combined with aspirin.

Side Effects, Complications, and Cautions for Antiemetics

Ondansetron side effects, complications, and cautions: Hypotension, headache, constipation, elevated liver function tests (LFTs), and short-lasting QT prolongation. Metabolism is by liver and kidneys; hepatic oxidative metabolism accounts for more than 95% of clearance from the body. Clearance decreases and half-life increases in patients with severe hepatic insufficiency.

Ondansetron ODT: To be opened immediately prior to use by peeling the foil blister backing completely off the blister rather than pushing it through the foil, and then placed on the tongue and allowed to disintegrate, after which it should be swallowed with saliva. Note that this tablet contains <0.03 mg of phenylalanine.

Droperidol side effects, complications, and cautions: Sedation, dizziness, anxiety, hypotension, QT prolongation, extrapyramidal symptoms (EPSs), and torsades de pointes (high doses). The drug contains a black box warning, necessitating a specific hospital policy for use. Monitor with electrocardiogram (EKG) for 2–3 hours.

Metoclopromide side effects, complications, and cautions: Drowsiness, diarrhea, and EPSs. Metoclopromide is excreted principally through the kidneys; thus, in those patients with a creatinine clearance below 40 mL/min, the dose should be halved. The drug undergoes minimal hepatic metabolism and is safe in patients with hepatic insufficiency.

Treatment of EPSs: EPSs are various movement disorders; usually in the context of droperidol or metoclopromide, acute dystonic reactions, caused by the blockade of dopamine receptors in the basal ganglia. Patients may exhibit stiffness or tremor, and muscle spasms of the face, tongue, or jaw: an "angry" facial grimace, torticollis, and oculogyric crisis. An observer might describe the child as angry and uncooperative. The first-line of treatment is diphenhydramine, which also has antiemetic and sedative effects. The pediatric dose is 2–5 mg/kg for patients of <12.5 kg and 25–50 mg for patients of >12.5 kg.

Complications of Local Anesthetics

Major local anesthetics complications can be categorized as allergic and toxic. Although rare, local anesthetic toxicity can be dangerous and potentially fatal. The danger of toxic blood levels has been well recognized since the introduction of cocaine, and although techniques of regional anesthesia have evolved, local anesthetic toxicity is still a major concern.

Allergic Reaction to Local Anesthetics

It is quite common for patients to describe an allergy to local anesthetics. However, upon careful history taking, most reactions are determined to be either syncope or vagal reaction in nature, often as a response to the needle injection, or palpitations as the result of epinephrine absorption.

True allergic reaction can occur as a result of the following three components of local anesthetics: the ester or amide group itself, the preservative sometimes used in multiple dose vials (methylparaben), or the antioxidant used in some formulations. The antioxidants (sodium bisulfite and metabisulfite) are usually used with products that contain vasoconstrictors to prevent biodegradation by oxygen. The ester group of local anesthetics is associated with a higher

incidence of allergic reaction due to its para-amino benzoic acid (PABA) metabolite. Allergic reaction to amide local anesthetics is very rare. Cross-sensitivity between ester and amide local anesthetics is extremely uncommon.

A hypersensitivity reaction is more challenging to diagnose when a patient is under general anesthesia. Self-limiting skin manifestations, urticaria, pruritus, and facial edema are the most common reactions without any further sequelae and can be treated with histamine H1 antagonists. In many cases, no treatment is needed. Bronchodilators may be required if the cutaneous reaction is followed by pulmonary bronchoconstriction.

Anaphylactic shock, characterized by hemodynamic collapse, is a life-threatening reaction that can be fatal if not treated. The anaphylactic response is mediated by a Type I hypersensitivity reaction in which immunoglobulin E (IgE) antibodies react with the allergen. In response, vasoactive mediators, histamine, leukotrienes, basophil kallikrein (BK-A), and platelet-activating factor are released into the bloodstream. The hemodynamic response occurs because of both systemic vasodilatation and increased capillary permeability. Bronchoconstriction and mucosal edema of the lower airways and swelling and angioedema of the upper airways are typical. Under endotracheal anesthesia, in addition to tachycardia and severe hypotension, an abrupt dramatic decrease in end-tidal CO_2, as a result of a decrease in cardiac output and pulmonary perfusion, is a major finding that strongly supports the diagnosis.

Anaphylactoid reaction, as the name implies, resembles anaphylaxis but is not IgE mediated and does not require prior introduction of the antibody. The reaction occurs as a result of mast cell activation by a particular drug. As a result, histamine release and complement activation occur. Distinguishing between anaphylaxis and anaphylactoid reaction is difficult and has no importance during the acute phase, since both reactions are treated in a similar way. Tryptase will usually be elevated in anaphylactic but not in anaphylactoid reaction.

The treatment in the OR starts with administration of 100% oxygen, 20 mL/kg IV fluid bolus, and discontinuation of the offending drug. The epinephrine dose is determined by the severity of the reaction, but usually 0.01 mg/kg IV epinephrine (maximum single dose of 0.1 mg) is needed and can be repeated every 5–10 minutes. Some authors advocate the administration of 0.05 mg/kg IM of epinephrine in addition to the IV dose in order to maintain a sustained blood level. A continuous epinephrine infusion may be needed as well, depending on the severity of the response.

Other drugs recommended during anaphylactic shock are an H1 blocker (diphenhydramine, 1 mg/kg IV up to 50 mg, or aminophylline, 5–6 mg/kg IV over 30 minutes), an H2 blocker (ranitidine, 1 mg/kg IV up to 50 mg, or famotidine, 0.5 mg/kg IV for children 1 year old or older), and steroids (methylprednisolone, 1–2 mg/kg IV, or hydrocortisone, 1 mg/kg IV).

Local Anesthetic Toxicity

Local anesthetic toxicity occurs as a result of a systemic overdose that can result in central nervous system and hemodynamic insult or hematologic consequences (methemoglobinemia).

Local anesthetic toxicity is a dose-dependent complication and can occur as a result of continuous absorption of the drug from the interstitial space after regional nerve block or from an inadvertent IV injection, even if the dose given is less than or equal to the maximum recommended dose. Toxicity depends on many variables, such as total dose of injection, rate of uptake, technique of administration, protein binding, lipid solubility, acid–base status, liver and renal function, and vascularity of the injection area (intercostal > caudal > epidural > brachial plexus > sciatic or femoral).

For regional anesthesia, the maximum recommended dose of lidocaine for infants and neonates is 7 mg/kg with epinephrine and 5 mg/kg without epinephrine.

The maximum recommended dose of bupivacaine is 1.5–2.0 mg/kg for neonates and 2.5 mg/kg for infants. An easy approximation for bupivacaine is 1 mL/kg of 0.25%, reduced by one-third for infants younger than 6 months of age.

Adding epinephrine to bupivacaine makes only a small change in the maximum recommended dose but is helpful for the diagnosis of inadvertent IV test dose injection.

A stereoselectivity of bupivacaine has been reported. The R(+) isomer blocks sodium channels more rapidly and more strongly than the R(−) isomer. This phenomenon can explain the greater cardiac toxicity of bupivacaine compared with that of ropivacaine.

Special attention and care should be taken when local anesthetics are administered to a severely ill child who has congestive heart failure or hepatic insufficiency. The dose should be calculated according to lean body weight rather than actual weight.

If a larger volume of local anesthetic is required, a lower concentration should be used.

The mechanism of action of local anesthetics is by blockade of sodium channels and limiting the initial upstroke of the action potential and its propagation. In addition, bupivacaine inhibits outflux of the potassium current, which results in prolongation of the action potential.

The classic description of local anesthetic toxicity is that of an exaggerated propagation of symptoms, both neurological and cardiovascular. Neurological symptoms are initial excitation that progresses to central nervous system depression. The patient who is old enough to describe symptoms initially describes tinnitus, metallic taste, tingling, dizziness, confusion, dysphoria, and numbness around the mouth. If not treated, these symptoms progress to agitation, motor twitching, seizures, loss of consciousness, coma, and respiratory arrest. Seizure is the most common symptom of local anesthetic toxicity and occurs 68% of the time.

Cardiovascular symptoms start with a short phase of hypertension and tachycardia that progresses to ventricular ectopy, ST changes, change in T wave configuration, dyspnea, QRS widening, hypotension, ventricular tachycardia, ventricular fibrillation, bradycardia, and asystole.

While the first symptoms of lidocaine toxicity are neurological, followed by cardiovascular symptoms if the dose and rate are high enough, the neurological symptoms of bupivacaine toxicity are followed immediately or appear simultaneously with cardiovascular symptoms. The lack of neurological prodrome plus the longer half-life

of bupivacaine explains the higher likelihood of adverse outcome with bupivacaine toxicity.

In neonates and infants, early signs of toxicity may be easily missed or misdiagnosed as inappropriate pain relief. Local anesthetic toxicity is even more challenging to diagnose in the anesthetized child. Thus, occurrences of any problems or symptoms after local anesthetic administration or infusion should always raise the question of toxicity.

Treatment of Local Anesthetic Toxicity

Local anesthetic injection should be stopped and help should be summoned immediately.

Local anesthetic toxicity treatment can be divided into supportive and definitive types.

Supportive Treatment

The airway should be secured and maintained, preferably with an endotracheal tube. Administration of 100% oxygen and hyperventilation to increase plasma pH is warranted. Seizure control can be achieved with benzodiazepines or propofol in small incremental doses. In case of circulatory arrest, cardiopulmonary resuscitation should be started using standard protocols. Arrhythmias should be managed per the same pediatric advanced life support (PALS) protocol, recognizing that arrhythmias may be refractory to treatment. Cardiopulmonary bypass should be considered. If circulatory arrest does not present, conventional therapies may be used to treat hypotension, bradycardia, or tachyarrhythmia. Most cases can be resolved with supportive measures only.

Definitive Treatment

In case of severe toxicity, IV lipid emulsion should be initiated (propofol is not a suitable substitute for lipid emulsion). The initial dose of IV 20% lipid emulsion, 1.5 mL/kg, should be administered promptly. (This means that IV lipid emulsion should be immediately available when local anesthetics are administered.) Thereafter, a continuous infusion of 20% lipid emulsion at 15 mL/kg/hour should be initiated.

However, if cardiovascular stability has not been restored after the initial bolus of lipid, up to three repeated lipid emulsion boluses every 5 minutes are required. The infusion dose can be increased to 30 mL/kg/hour if cardiovascular stability has not been restored. (The authors' experience suggests that giving too much is less risky than not giving enough.) Neonates and infants may require higher bolus doses up to 3 mL/kg. Chest compressions should be continuously performed if a nonviable cardiac rhythm exists until resolution of dysrhythmias with effective cardiac output.

There is laboratory evidence that epinephrine and vasopressin may impair resuscitation during local anesthetic toxicity. Therefore, epinephrine should be used in low doses for treating hypotension if it is refractory to other measures, and lipid emulsion should be initiated as soon as possible during resuscitation in cases of severe toxicity.

Risk Reduction

Use the lowest dose of local anesthetic. Always consider comorbidities, metabolic status, and medications used by the patient (sodium channel inhibitors), and reduce the local anesthetic dose accordingly. Consider the use of intravascular markers (epinephrine mixed with local anesthetic will cause tachycardia, indicating that the local anesthetic has also entered the bloodstream) and a test dose. Aspirate prior to each injection while observing for blood. Inject by smaller incremental doses. Continue to be alert for local anesthetic toxicity, as local anesthetic can continue to be absorbed from the site of injection.

Methemoglobinemia

Oxidation of ferrous [Fe^{2+}] iron to ferric iron [Fe^{3+}] results in methemoglobin. Methemoglobin has a decreased ability to bind oxygen and a greater affinity to bound oxygen, which shifts the hemoglobin dissociation curve to the left. Symptoms of methemoglobinemia are proportional to methemoglobin concentration and are limited to skin and blood color appearance when the concentration is less than 15%. When the methemoglobin concentration exceeds 15%, neurologic and cardiac symptoms occur due to cellular hypoxemia. A methemoglobin level of more than 70% is fatal.

During normal physiologic conditions, when the methemoglobin level is less than 1%, methemoglobin is converted back to its ferrous state by nicotinamide adenine dinucleotide (NADH) cytochrome b_5 reductase. This system is overwhelmed when there is an excess level of methemoglobin and hypoxemia results.

Two-wave pulse oximetry shows an oxygen saturation (SpO_2) of 85% since the methemoglobin absorption ratio for 660–940 nm wavelengths is 1. Diagnosis can be confirmed with a multiple-wavelength co-oximeter. Classically, the blood color is described as chocolate brown.

Local anesthetics known to induce methemoglobinemia when used in excess are prilocaine (used topically as EMLA cream), lidocaine, benzocaine (hurricane spray), and bupivacaine. It is easier to reach toxic levels in children because of their low body weight.

The maximum recommended pediatric dose for prilocaine is 2.5 mg/kg.

The maximum EMLA application area for neonates of <3 months is 10 cm^2; for infants of 3–12 months, 20 cm^2; for 1- to 6-year-olds, 100 cm^2; and for 7- to 12-year-olds, 200 cm^2. However, a patient's weight may not always be proportional to his or her age, and this must be considered in determining the maximum dose for an individual patient.

The maximum application time is 4 hours, except for neonates, where the application time should not exceed 1 hour.

Treatment of Methemoglobinemia

Treatment is based on oxygen supplementation and methylene blue. The dose for 1% methylene blue solution is 1–2 mg/kg intravenously over 5 minutes. This dose can be repeated in 30–60 minutes depending on clinical response. Treatment with methylene blue uses an existing minor metabolic pathway, the nicotinamide adenine dinucleotide phosphate (NADPH)–methemoglobin reductase system, to convert methemoglobin back to hemoglobin.

Methylene blue cannot be used to treat methemoglobinemia in patients with glucose-6-phosphate dehydrogenase (G-6PD) deficiency because G-6PD is needed in the conversion pathway. Symptomatic methemoglobinemia

can be treated in these patients with exchange transfusion. Hyperbaric oxygen has also been used.

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CHAPTER
10

Office Pediatric Urology

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INTRODUCTION

The environment of a medical office can play a pivotal role in making pediatric patients and their families comfortable. Engaging decorations, bright colors, toys, and play areas often help calm nervous children. A bulletin board with patient photos and cards may soften the feel of the office. Every effort should be made to allow parents to be with their child at all times to provide reassurance. Each physician's style and personality is different, but often those who deal with children usually forgo the formality of a white coat so that the encounter might be more familiar to the patient. It is important upon entering the examination room to first engage the patient in gentle conversation, when possible, to develop rapport and place the child at ease. If the child is old enough, history taking generally begins with the child and is supplemented by parental input.

The physical examination is generally performed on the examining table with a parent standing beside the physician at the head of the bed. It is important to let the child know that he or she will not be poked or hurt but gently checked. As children approach puberty, they may be relieved to have one or both of their parents leave for the examination when given this opportunity by the physician. After the exam is completed, it is generally important to let the patient know that he or she is finished so that he or she will no longer be ill at ease. Upon leaving the office, children are often rewarded for their good behavior so they will look forward to return visits.

Most physicians find that dealing with children in an honest, straightforward manner is best. It is appropriate to tell the child before any uncomfortable or painful procedures are undertaken so that he or she will not fear the entire time, but only the first few moments that it occurs. Surprising a child with an unpleasant exam or injection results in a loss of trust and faith in the physician, which is difficult to regain. Parents are encouraged to tell their children honestly about diagnostic x-ray examinations and office visits so that the children can be appropriately prepared. Under these circumstances, the exam and history may be completed accurately with little threat to the child.

FORESKIN AND PHIMOSIS

The appropriate management of penile problems in childhood is based on an understanding of genital embryology and postnatal penile development. Genital differentiation takes place between the 9th and 13th weeks of gestation. The glans penis forms from the genital tubercle and is covered with a prepuce that is adherent to its surface. The preputial attachments persist throughout gestation, and the epithelial layer of the inner prepuce and the glans penis are fused at birth. The newborn foreskin cannot be retracted without disrupting this natural adherence. Subsequently, glandular secretions and desquamated epithelial debris, collectively called smegma, collect between the inner prepuce and the glans penis, gradually separating these two layers. The buildup of this material can be impressive, and patients may present with a mass that can be seen through the thin foreskin. This has been referred to as a foreskin pearl. Treatment is not required, as the smegma eventually erupts at the foreskin meatus, disrupting the adherence and resulting in partial separation of the foreskin.[1] This sequence is often misdiagnosed as a penile infection, and the smegma is presumed to be "pus." Hopefully, physicians easily recognize that this is not an infection but the physiologic appearance of smegma. Reassurance usually quiets parental concerns.

The physiologic adherence (physiologic phimosis) resolves spontaneously, but may remain present for several years. Texts suggest that most physiologic phimosis resolves by the age of 3–5 years, such that the glans penis can be fully exposed.[2] In the authors' experience, limited adherence is of little significance and may remain for years longer. In a longitudinal study, Oster[3] reported that physiologic phimosis in school-aged boys resolved over time (Table 10.1).

Physiological phimosis should be distinguished from pathologic or true phimosis. Physiologic phimosis exists when the adherence between the inner prepuce and glans penis persists as filmy attachments (Figure 10.1). True phimosis occurs when the foreskin cannot be retracted after it has been previously retractable, if there is a densely thickened prepuce that will not retract, or when foreskin

TABLE 10.1 Incidence of phimosis in children

Age (Years)	Phimosis (%)	Tight Prepuce (%)
6–7	8	1
8–9	6	2
10–11	6	2
12–13	3	3
14–15	1	1
16–17	1	1

FIGURE 10.1 Physiologic phimosis. This prepuce displays normal healthy-appearing circumferential tissue, with no evidence of scar or contracture.

remains nonretractile after a patient has completed pubertal development.

The easiest way to differentiate physiologic phimosis from pathologic phimosis is careful examination. Forceful separation of foreskin adhesions is not recommended because of pain and trauma to the patient, but gentle proximal traction of the foreskin may enable one to differentiate between normal and abnormal. If the foreskin retracts part way and then lies flat against the glans penis and effaces or thins, the remaining attachments are likely physiologic and more time is required for natural separation to occur. If, when the foreskin is retracted to the point of attachment, a thickened, rolled edge is seen, then this is likely pathologic phimosis due to scarring and inflammation (Figure 10.2). Ballooning of the foreskin during voiding is often associated with true phimosis as well. Phimosis is unlikely to resolve on its own and may require circumcision. There have been recent studies suggesting that steroids applied to the prepuce and glans penis will help separate physiologic adhesions, aiding in the resolution of this diagnostic dilemma.[4–7]

Questions often arise about care of the uncircumcised penis. The genital area should be cleaned as any other skin area, and the foreskin may gently be retracted to the extent allowable without discomfort for cleaning. Forcible retraction may result in tearing of the foreskin meatus, inflammation, and secondary scarring leading to true phimosis.

POSTCIRCUMCISION PHIMOSIS (ENTRAPPED PENIS)

Following routine neonatal circumcision with any standard circumcision clamp, an unusual type of secondary phimosis can develop. Since the circumcision scar is circumferential, and the process of wound healing involves contracture, this may cause narrowing of the shaft skin at the circumcision site. If the circumcision site is mobile and sufficient inner foreskin remains, the circumcision site can migrate distally over the glans and begin to contract in this position (Figure 10.3). This contraction and scarring may

FIGURE 10.2 This prepuce displays a true 'phimotic ring' laterally and inferiorly with thickened skin, whereas superiorly the skin shows a more normal, effaced (thin) appearance when the foreskin is pushed gently toward the base of the penis.

be tight enough that the glans penis can no longer be seen and occasionally urinary flow may be restricted. This type of phimosis (penile entrapment, secondary phimosis) can be avoided by firmly seating the bell of the newborn clamp at the coronal margin so that there is not redundant inner prepuce remaining, which might let the circumcision scar ride distally over the coronal margin. This seems to be a more common problem in young boys with an abundant pubic fat pad who may not be candidates for circumcision in the first place (Figure 10.4). If secondary phimosis is discovered early after circumcision, aggressive foreskin retraction by stretching the ring with a hemostat dilates the scar and the need for later revision of the circumcision is avoided. In other cases, the phimotic ring may be anesthetized and snipped in the office, incising vertically and closing horizontally to create a wider circumference. This may not resolve the problem in all patients, and formal circumcision revision may be necessary in some, reducing the inner foreskin length so that the circumcision scar cannot migrate past the coronal margin; occasionally, removal of more shaft skin becomes necessary. Some authors have reported the use of topical steroid cream for the treatment of postcircumcision phimosis, yielding complete resolution in a majority of patients.[8]

FIGURE 10.3 Entrapped penis following circumcision (secondary phimosis).

FIGURE 10.4 Severe penile entrapment. This required incision of the phimotic ring in two locations followed by horizontal closure of the vertical incision lines.

PENILE GLANULAR ADHESIONS (SKIN BRIDGES)

After newborn circumcision, the glans epithelium is denuded owing to separation of the physiologic adhesions with the foreskin. The circumcision site is also a raw surface, and if the glans epithelium and the circumcision site rest together for a prolonged period, a postsurgical adhesion may form (Figure 10.5). These are dense adhesions that cannot be teased apart in the office. These adhesions usually occur as skin bridges so that an instrument tip can be passed underneath them, and their blood supply comes from both the shaft skin and the glans. Surgical division of such skin bridges is required.

This usually requires some sort of analgesic agent, which may be EMLA® cream (2.5% prilocaine and 2.5% lidocaine; Astra Pharmaceuticals, Westboro, Massachusetts), or local injection in the office, or if more extensive, general anesthesia. After appropriate analgesia, a hemostat is used to crush the bridge near the glans and the adhesion is divided with scissors, rotating the blade and cutting the skin bridge nearly flush with the glans epithelium. Sometimes a second cut flush with the shaft skin will be necessary for good cosmesis. It is important not to cut the skin bridge in the middle because this often leaves a skin tag of shaft skin on the glans penis, which is a noticeable cosmetic problem. Suturing may be necessary for bleeding or wound approximation. Ointment is then placed on the penis twice daily for 7–10 days; gently retracting the shaft skin prevents the two edges from coming into contact to reform the adhesion.

PARAPHIMOSIS

Paraphimosis is the term applied when the foreskin that has been retracted cannot then be brought back over the glans penis (Figure 10.6). This can happen after the foreskin has been forcefully separated for the first time, disrupting the preputial adherence to the glans. In the hospital, this often occurs when the foreskin has been retracted for the placement of an indwelling catheter. Once the catheter has been secured, medical personnel neglect to replace the foreskin over the glans penis. With the tight foreskin proximal to the glans penis, venous congestion leads to progressive swelling. When paraphimosis is recognized, it is imperative that the foreskin be immediately placed back over the glans to allow the blood flow to return to the prepuce and glans. If there is significant edema, this can be difficult. The best technique

FIGURE 10.5 Postcircumcision skin bridges.

is to hold a gauze sponge with the index and third fingers of each hand proximal to the foreskin, with the gauze covering the fingers for traction. The thumbs push the glans penis back through the paraphimotic ring between the other four fingers that are supporting it. A minute or two of steady pressure may be required to decompress the glans and force the foreskin edema proximally and allow for the glans to suddenly slip through to the paraphimotic ring. Placing ice on the penis before this procedure has been advocated, and a penile anesthetic block may be administered before the manual reduction. Additionally, infiltration of the edematous foreskin with hyaluronidase has been reported to facilitate decompression via dispersing extracellular edema, thus permitting easy reduction of the foreskin.[9] Briefly, approximately 1 mL of hyaluronidase (150 U/cc available as Wydase; Wyeth-Ayerst Laboratories, Philadelphia, Pennsylvania) is injected into several sites in the edematous prepuce using a fine-gauge (≤27 g) syringe followed by gentle, circumferential pressure. The edema will resolve almost instantaneously such that the paraphimosis can be reduced.

Some authors have also reported the use of granulated sugar as an effective and safe technique to reduce paraphimotic foreskin edema.[10] If manual reduction is unsuccessful, immediate dorsal slit of the tight preputial ring will restore venous drainage from the distal tissue. A formal circumcision can be completed at a later date if necessary.

FIGURE 10.6 Paraphimosis with edematous, discolored prepuce trapped proximal to glans penis.

MEATAL STENOSIS

Stenosis of the urethral meatus seems to be largely an acquired problem of circumcised boys. Recurrent meatitis or meatal inflammation secondary to prolonged exposure of the meatus to the moist and irritating environment of the diaper (ammoniacal dermatitis) or other inflammatory skin diseases can induce this problem. The delicate meatal skin edges lose their superficial epithelial lining when inflamed, and as a result become adherent in a side-to-side fashion. This almost always occurs ventrally and progresses dorsally, and boys are left with a small or even pinpoint meatus at the apex of the glans. Some authors have suggested that the advent of disposable diapers has led to an increasing prevalence of this problem since the 1980s. The occurrence of meatal stenosis is distinctly unusual in an uncircumcised boy, and therefore is best considered a potential side effect of circumcision.

Causes beyond simple irritation that can induce strictures of the meatus include prior hypospadias repair or other penile surgery, prolonged urethral catheterization, trauma, or balanitis xerotica obliterans (BXO). These diagnoses are often apparent on examination or when reviewing the child's history. BXO induces a characteristic whitish circumferential discoloration of much of the glans and may induce a narrowing of the urethra extending more proximal than simple irritative meatal stenosis. BXO is more difficult to treat.

Normal meatal caliber based on age has been reported in boys. In general, a boy under the age of 1 year should have a meatus that easily accepts a 5-French feeding tube. Between the ages of 1 and 6 years, this increases to at least an 8-French size. It can be difficult to estimate meatal size accurately when inspecting this visually. However, gentle lateral traction on the meatal edges to open the meatus side to side reveals the typical fused appearance of the ventral edges, confirming some degree of stenosis. On the other hand, if normal urethral mucosa can be everted, meatal size is probably accurate. Final confirmation is obtained by observing voiding. There is a characteristic dorsal deflection of the stream due to a ventral lip of scar tissue as a result of fusion of the meatal edges. The patient also demonstrates a very fine-caliber, forceful stream with a long voiding distance. This is due to the acute decrease in the size of the lumen of the urethra distally and the secondary accelerated velocity of the urine. Some patients

FIGURE 10.7 Vertical incision for meatotomy following 60 seconds of clamping with a hemostat.

will learn to direct their penis toward their feet during voiding so that the stream will enter the toilet bowl, while others seem not to catch on and miss the bowl entirely.

Meatal stenosis is uncommonly diagnosed prior to a boy becoming toilet trained. There may be intermittent dysuria with discomfort at the tip of the glans and occasional blood spotting in the underwear due to recurrent inflammation at the meatus. Patients with meatal stenosis demonstrate a prolonged voiding time, and some boys decide that it is simpler to sit during voiding rather than try to direct their streams while standing. It should be noted that meatal stenosis is an unlikely cause of recurring urinary tract infection (UTI) or true obstruction to the lower urinary tract. When the history, exam, and observation of the urinary stream suggest meatal stenosis, no other diagnostic evaluation is required.

When any of the above symptoms are present, and voiding is characteristic, treatment of meatal stenosis is generally warranted. Simple dilatation of the urethral meatus will often result in tearing of the skin edges and a high rate of recurrent stenosis. Urethral meatotomy is therefore the preferred method of treatment. Meatotomy is a very simple procedure in which one prong of a hemostat is inserted within the urethral meatus and directed toward the ventrum in the midline of the glans a few millimeters proximal to the stenotic pinpoint meatus. The skin edges are crushed together for 1–2 minutes. Once the clamp is removed, fine scissors are used to incise the ventral midline, thus reopening the meatus (Figure 10.7). The crushed skin remains together, generating appropriate hemostasis.

Options exist in terms of anesthetic techniques for meatotomy. The procedure may be performed under a general anesthetic in the operating room as a quick and simple outpatient procedure; however, this is generally not necessary. Some urologists have performed this procedure in an office setting by injecting a small amount of lidocaine with epinephrine directly into the ventral meatal skin using a small-caliber needle. This provides analgesia and hemostasis. However, most boys will not tolerate this since the injection is distinctly uncomfortable.

The authors have reported using topical EMLA cream (eutectic mixture of local anesthetics) applied over the entire glans to anesthetize the meatus and perimeatal skin for urethral meatotomy.[11,12] Others have recently reported a similar use for EMLA cream.[13] The EMLA cream is applied liberally over the entire glans, especially on the ventrum. It is secured in place with an occlusive dressing and left in contact with the glans skin for 1–1.5 hours before the procedure (Figure 10.8). The cream is removed and the meatotomy is completed. The vast majority of patients experience no discomfort when EMLA cream

FIGURE 10.8 EMLA cream is applied over entire glans prior to meatotomy. This remains for at least 60 minutes before the procedure.

is used with this technique. Occasionally, there will be a sensation of pressure when the hemostat is clamped. This is almost always at the most proximal point of clamping. In an occasional patient, the EMLA cream may be supplemented with a small amount of injected lidocaine with epinephrine, which seems to be minimally uncomfortable when given following EMLA. Uncommonly, a patient may require a suture on each side of the meatotomy for oozing from the meatal edges following the procedure.

Patient tolerance of the procedure overall is quite good as long as a caring and patient approach is taken to reassure boys before and during the procedure. The room is quiet with minimal lighting, and parents bring some of the child's books and handheld toys for the waiting period after the EMLA is applied. Parents stay in the room during the procedure, and this further reassures the child. The authors have chosen, based on parental preference and patient personality, to use midazolam hydrochloride as an anxiolytic with good results in some patients. However, the general observation has been that midazolam is unnecessary for the majority of patients.

Following meatotomy, it is crucial to keep the edges of the meatus separated so that restenosis does not occur. Immediately following meatotomy, while still in the office, the parent is shown how to apply antibiotic ointment within the meatus. The parent then continues this at home, using one hand to separate the meatus, while the index finger of the other hand is used to place a small amount of ointment directly into the meatus. This is continued twice daily for the first 2 weeks and then once daily for another 4 weeks. Alternatively, a small tube of ophthalmic ointment (Lacri-Lube) may be used as a meatal dilator. A small amount of the ointment is extruded from the metal tip for lubrication, and the tip is then passed within the meatus. It is of appropriate size to serve as a dilator for most boys undergoing meatotomy. The use of meatal dilation may be helpful in certain cases if readherence of meatal edges is problematic, but the authors do not feel that it is routinely required.

Patients may be expected to experience mild dysuria for the first 1–2 days postoperatively. It has generally been helpful to have them take ibuprofen or acetaminophen 2 hours preoperatively to decrease discomfort. Boys at the age of 3 or 4 years may respond to meatotomy by holding the urine for prolonged periods of time. Placing them in a warm tub often stimulates voiding in this circumstance. One value of keeping ointment over the meatal edges is that it functions as a barrier to shield the surface from the passage of urine and the resulting discomfort. It should also be noted that increasing the fluid intake for the first day or two following the procedure dilutes the urine and leads to less dysuria. Minor blood spotting in the underwear following meatotomy is common for 1–2 days. Printed handouts are given to parents with these recommendations, and they are warned of the risk for restenosis when the instructions are not followed. In addition, boys who remain wet following meatotomy, from either still being in a diaper or having problems with persistent incontinence, are at risk for redeveloping stenosis based on recurrent inflammation of the meatus. This group may not be candidates for treatment until dryness is achieved. Two out of 226 patients seen by the authors required a second meatotomy. Over the same period that they have used EMLA cream for analgesia, the authors have chosen to perform meatotomy in the operating room in three boys due to patient behavioral issues, including extreme attention deficient disorder. As experience has been gained, it has become apparent that midazolam works well in the moderately, overactive, anxious, or difficult young boy, and meatotomy in the operating room should be reserved for the patient with BXO of posthypospadias meatal stenosis.

NONNEONATAL CIRCUMCISION

The pros and cons of newborn circumcision have been and will continue to be debated. Less discussion surrounds circumcision after the newborn period, when it is estimated that 1 in 100 uncircumcised boys will require circumcision.[14] During childhood, the most common indication for circumcision is phimosis. This develops because of preputial irritation leading to inflammation, scarring, and thickening of the preputial opening so that the foreskin cannot retract. Hygiene then becomes a problem, and occasionally, this process is so severe that urine flow is affected and the preputial sac dilates with urine dribbling out after voiding. In some patients with chronic skin irritation and inflammation, fissures of the prepuce develop. This makes spontaneous erections and retraction of the foreskin painful, and discomfort occasionally awakens the patient during sleep. Steroid ointments may reduce inflammation, but circumcision is indicated if fissures persist.

Balanoposthitis is an infection of the glans and preputial sac. This infection occurs uncommonly, but can be painful. Skin floras are usually the predominant organisms found on culture. If the balanoposthitis is mild, sitz baths and topical antibiotic ointment (bacitracin) may be sufficient. If cellulitis and/or fever are present, then a systemic antibiotic is added. The first episode of balanoposthitis is not a mandatory indication for circumcision. Recurrent episodes strengthen the argument for circumcision. Penile hygiene should be reviewed with the parents and patient.

UTIs are more common in uncircumcised boys, especially during the first 6 months of life.[15] Some consider a UTI in a boy an indication for circumcision. After 1 year of age, the increased risk for UTI in the uncircumcised male diminishes.

Penile cancer is known to be prevented by newborn circumcision. It is thought that the development of penile cancer closely correlates with penile hygiene, and in developed countries where hygiene is good, the rate of penile cancer is very low regardless of circumcision status. Since penile cancer is very uncommon, the likelihood of a serious circumcision complication may be higher than the eventual possibility of penile cancer.

Occasionally, trauma to the prepuce leads to circumcision. Zipper trauma is the most common occurrence. Usually, with local anesthesia, the zipper can be dislodged by simple advancement or at times by cutting the median bar of the zipper, thereby allowing the teeth to separate. Occasionally, circumcision may be warranted acutely.

After the newborn period, the indications for circumcision are relatively few. Circumcision is generally performed under general anesthesia after the newborn period, although the use of local blocks and circumcision

in boys beyond this period has been reported.[16] Depending on the age of the patient and the size of the penis, surgical excision and suturing or newborn clamps may be used. The procedure is usually successful with low complication rates and is performed on an outpatient basis. Recovery is generally prompt, with older patients experiencing more discomfort and having a longer recovery period.

GENITAL HOLDING

Children who hold or clutch their genitalia are often of concern to their parents. This behavior begins shortly after toilet training and may last through the prepubertal years. It is more common in boys than girls. In boys, some degree of genital holding is almost universal. This behavior is thought to have no significant sexual or psychological implications[1] and is thought to be normal and does not warrant any diagnostic studies. Seldom is there any underlying physical cause, and evaluation beyond physical examination and urinalysis (UA) is not warranted. The best advice for parents is to have them redirect the child's attention without placing great emphasis on this behavior. Generally, over time, children learn more acceptable public behavior without the apparent preoccupation for genital holding. Occasionally, very persistent holders may be told that the behavior may make others uncomfortable, and that for this reason, if they must hold themselves, they should do this in private. Parental education and reassurance is the best course of management.

URETHRAL PROLAPSE

The circumferential eversion of urethral mucosa through the urethral meatus may be seen in girls and is termed urethral prolapse. It is associated with vascular congestion and possible strangulation of the prolapsed tissue. It is possible to have a partial or incomplete prolapse, but complete urethral prolapse is more common.[17] The etiology of urethral prolapse is unclear. Suggested causes include poor attachment between the inner longitudinal and outer circular and oblique smooth muscle layers of the urethra associated with antecedent episodes of increased abdominal pressure, mucosal redundancy and vaginal mucosal atrophy, estrogen deficiency leading to lax periurethral fascia, neuromuscular disorders, urethral malposition, increased width of the urethra, poor bladder support, and deficient elastic tissues.[18] Predisposing Valsalva maneuvers, such as chronic coughing, asthma, and constipation, as well as UTI and trauma, have been reported.[19–22] Urethral prolapse is often misdiagnosed as the cause of urogenital bleeding in girls. The correct diagnosis at presentation has been reported in only 21% of cases.[23] It is important to recognize that the prolapse appears as a doughnut-shaped mass protruding at the vulva (Figure 10.9). The mucosa is edematous, friable, bright red, or blue-black. As time goes on, it may become infected, ulcerated, necrotic, or gangrenous.[17] The differential diagnosis of urethral prolapse includes a prolapsing ectopic ureterocele, a prolapsed urethral polyp, an ectopic ureter, a prolapsed bladder, a urethral cyst, hydrometrocolpos, condyloma acuminatum, sarcoma botryoides, and a periurethral abscess. The diagnosis of urethral prolapse is visual and based on the typical circumferential appearance of the lesion around the meatus. None of the other stated conditions have a similar appearance. At times, diagnostic confirmation is made by placing a catheter or an instrument tip demonstrating that the urethra is actually in the center of the edematous tissue. Imaging studies are not necessary, but a voiding cystourethrogram (VCUG) can show a narrow, distal urethra.[24] The age range at diagnosis in pediatric series is from 5 days to 11 years, with a mean of 4.5–6 years.[20,22,23,25,26] Urethral prolapse has been reported in identical twins.[27] There is a significant preponderance of urethral prolapse in patients of African descent, with reports being 90% or greater.[20,23,28] A recent study supports previously reported findings by other authors in terms of demographics and clinical presentation.[29]

FIGURE 10.9 Urethral prolapse: note the doughnut appearance with urethral meatus centrally.

In addition to bleeding, symptoms include dysuria or frequency in 25% of cases.[20,22,23,25] Nine percent of the patients are asymptomatic, with the urethral mucosa showing no tenderness.[17,22] Urogenital bleeding due to urethral prolapse may be mistaken to be from a vaginal source.[20,22,23,25,30]

Treatment options vary for urethral prolapse. Simple treatments should be tried first, including observation alone, topical antibiotic ointment, topical estrogen cream,

and sitz baths. Surgical treatments include primary excision, reduction and catheterization, and suture ligation of the prolapsed tissue over a catheter, and in adult women, cryoablation has been reported.[31] Most published series recommend conservative therapy.[20,23,25,29,30,32,33] Surgical treatment should be reserved for those rare instances of recurrence or persistent, symptomatic prolapse.[18,20,23,25,30]

LABIAL ADHERENCE

Labial adherence, midline fusion of the labia minora, is a common acquired lesion in young girls. Before puberty, the labia minora are covered with a thin hypoestrogenized epithelium.[28,34] An irritating event, such as infection, trauma, or inflammation, causes the area to become denuded and inflamed, and the medial labial surfaces adhere with a fibrinous exudate over their surfaces.[28] Perhaps the most common inciting event is ammoniacal irritation. Adherence generally begins posteriorly and progresses anteriorly, leaving a small opening for the urine just inferior to the glans clitoris (Figure 10.10).[35] Occasionally, the process begins near the clitoris, forming a preputial fusion.[28] Labial adherence is also known as labial adhesions, labial agglutination, gynatresia, vulvar fusion, coalescence of the labia minora, vulvar synechiae, labial fusion, and occlusion of the vaginal vestibule. Differential diagnosis includes scarring of the labia minora, imperforate hymen, vaginal agenesis, clitoral hypertrophy, or disorders of sexual differentiation.[34]

FIGURE 10.10 Labial adhesions characterized by fusion of the labia minora. There is generally a small opening anteriorly.

Labial adherence is fairly common and accounts for a large number of the genital abnormalities seen in girls. The peak incidence is between birth and 2 years old, and again around the age of 6–7 years, although fusion can be seen until puberty.[35,36] Most girls with fused labia are asymptomatic, but some have a deflected urinary stream or vaginal pooling of urine. Dysuria, generally secondary to the underlying inflammatory process, may be a persistent complaint. Patients may present with the diagnosis of UTI;[35,36] however, the suspected infection may simply be a contaminated specimen, as urine pools beneath the fused labia before exiting. True adhesion of the labia can occur in sexually abused girls with an incidence of approximately 3%.[34,37] This scarring is often thick and irregular in texture, and involves deeper layers.[38]

Treatment of adherent labia minora is not routinely required. Parents and referring primary care physicians should be reassured that they will lyse spontaneously given time. If treatment is thought to be necessary, estrogen cream can be applied daily, with success reported to be as high as 90% at 8 weeks.[34] The side effects of the estrogen cream will include vulvar pigmentation in all of the patients and breast tenderness in 6%, which resolves after the estrogen therapy is discontinued.[35] However, the long-term effects of estrogen given to prepubertal girls are unknown, along with potential malignancy risk; therefore, treatment beyond a few weeks is probably unwarranted. In an effort to avoid the side effects associated with application of estrogen cream, some have used 0.05% betamethasone ointment in one to three courses lasting 4–6 weeks each, with success in up to 68% of patients, including some in whom estrogen cream had been unsuccessful.[39] Persisting adherence can be separated in the office using topical anesthetic (EMLA) and gentle, blunt separation.[28,34,35] An oral anxiolytic may be considered in such girls for this procedure. Following separation, daily separation of the labia with application of an ointment should be continued for a time to prevent recurrence.[34,35] Forceful separation without analgesia is not recommended.

VAGINAL CYSTS

Incidental vaginal cysts are uncommon and are often found in the newborn period, possibly as a consequence of stimulation by maternal estrogens. They are usually single and between 1 and 3 cm in diameter. When recognized in newborns, evaluation should include passage of a catheter or instrument into the vaginal introitus to ensure patency. Rarely, ultrasonography (U/S) may be necessary to ensure that the vagina is normal and not obstructed. These cysts almost always rupture spontaneously or resolve over a few weeks and need no further treatment. Introital cysts are of several types, including Gartner's duct cyst, Müllerian duct cyst, and epithelial inclusion cyst.

Gartner's duct is the distal rudimentary portion of the Wolffian (mesonephric) duct in girls. These ducts in girls usually regress and almost completely disappear. If remnants persist, they are usually found along the anterolateral walls of the vagina. Flat, cuboidal cells line the cyst.[40]

Gartner's duct cysts present as a perivaginal mass and usually appear in infants.[41] These cysts can be large enough to protrude from the vaginal introitus or fill the vagina and block the opening.[37,41,42]

Müllerian duct cysts are remnants of nonfused portions of the Müllerian ducts. They are generally asymptomatic and do not usually cause problems until menarche.

Most epithelial inclusion cysts are remnants of the urogenital sinus. Following trauma or surgery, buried vulvar or vaginal epithelium may also cause epithelial inclusion cysts. These are rare in children, although not uncommon in older women.[40] They usually occur posteriorly and in the midline of the vagina.[43] The cysts contain thick caseous material with a squamous epithelium lining their inner surface.[40] Surgical excision is the treatment of choice.[42]

HYDROCOLPOS

Distension of the vagina with fluid or mucous secretions is called hydrocolpos. If the uterus is involved, the term is *hydrometrocolpos*. The vagina can be obstructed from an imperforate hymen, transverse vaginal septum, or atretic vaginal introitus.[44] This produces a bulging, shiny, pearly gray protuberance observed over the vaginal introitus.[41,43]

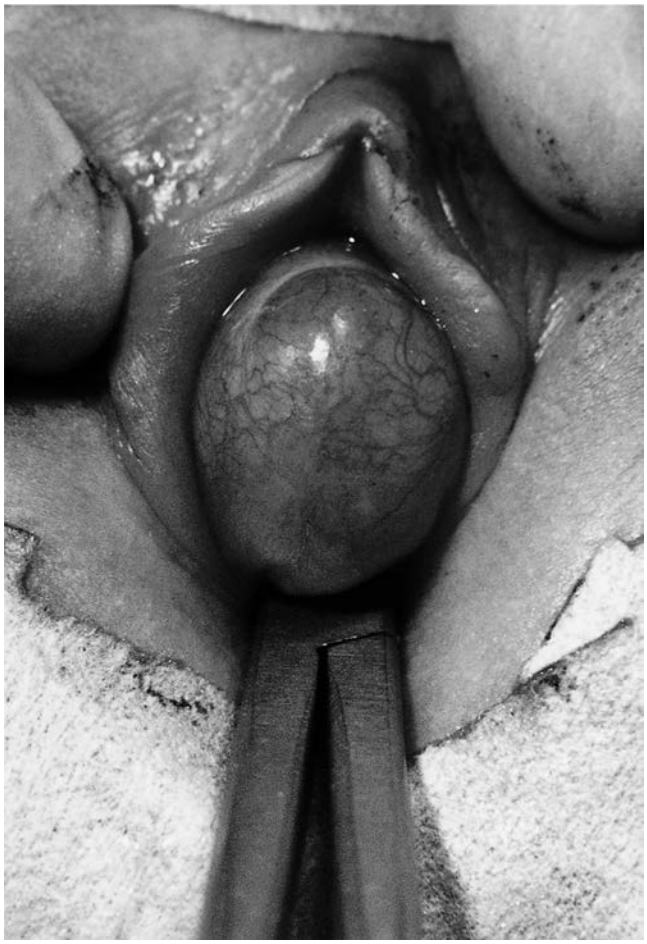

FIGURE 10.11 Hydrocolpos with duplicated vagina. The urethral meatus is seen splayed above the bulging mass while the hemostat is placed in the patent (second) vaginal opening.

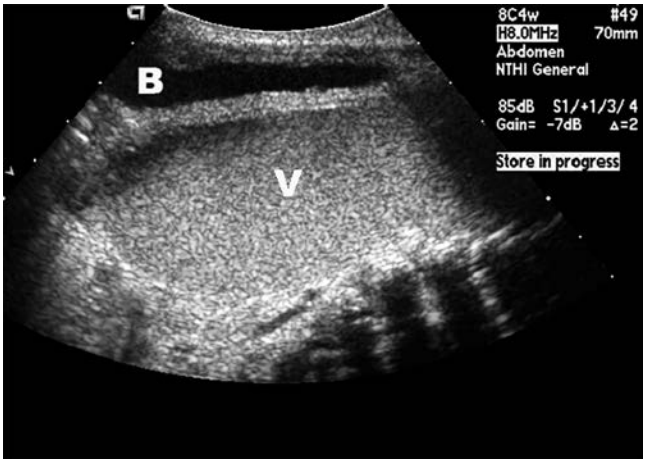

FIGURE 10.12 Ultrasonographic (longitudinal plane) image of hydrocolpos. Nondistended mildly thickened bladder wall (B) present anteriorly. Dilated vagina (V) with hyperechoic cellular and fluid debris present.

The urethral meatus can be noted anterior to the mass (Figure 10.11). Large abdominal masses can be palpable or identified on U/S (Figure 10.12). Occasionally, urinary retention can be due to a mass effect. U/S shows a retrovesical oval cystic mass occasionally causing hydroureteronephrosis.[45] Treatment consists of drainage of the obstructed vagina perineally, but occasionally temporary abdominal vaginostomy may be necessary.

OTHER INTERLABIAL MASSES

Periurethral cysts are known to occur along the distal one-third of the urethrovaginal wall.[40] The urethral meatus can be displaced, causing compression and a deflected urinary stream or dysuria. These cysts usually rupture spontaneously.[44,46]

VAGINITIS

Vulvovaginitis is the most common cause of vaginal bleeding in the pediatric age group.[47] Vulvitis is vulvar irritation secondary to trauma, topical allergens, mechanical irritation, chemical irritation, or poor hygiene.[48] Vaginitis is erythema and inflammation of the vaginal mucosa generally associated with discharge. Vulvovaginitis is very often a self-limiting problem and immediate workup is not necessary. As the symptoms persist or become more annoying, workup should include sampling of the vaginal pool for pH, wet mount, potassium hydroxide swab, and examination for chlamydia and gonorrhea. A UA with culture may be diagnostic. If specific treatment is desired, a definitive diagnosis must be made.[47] Noninfectious causes in infants and children should be investigated, including ruling out the presence of a foreign body. Foreign body vaginitis symptoms are similar to other types of vaginitis. Toilet paper remnants are the most common objects found in the vagina.

NONSPECIFIC VULVOVAGINITIS

Nonspecific vulvovaginitis refers to a nonpurulent, nonodorous discharge with a neutral pH and normal flora on wet mount. It accounts for 25%–75% of all vulvovaginitis seen in premenarchal girls.[46] The etiology includes poor hygiene, urinary soiling, tight clothing, or chemical irritants, such as harsh soaps. When testing is normal, treatment consists of reassurance and encouragement of good hygiene and appropriate clothing.

NEWBORN PHYSIOLOGIC LEUKORRHEA

It is normal for newborn girls under maternal estrogen stimulation to have a vaginal discharge. It is usually clear with white-gray mucus not associated with odor or irritation. Wet mount shows numerous epithelial cells without pathogenic bacteria or leukocytes. The discharge diminishes once maternal estrogen stimulation subsides. The tendency toward treatment with vaginal creams and antibiotics should be discouraged.

SEXUALLY TRANSMITTED DISEASES

A common sexually transmitted disease is chlamydia, caused by *Chlamydia trachomatis*, which is an obligate intracellular gram-negative organism capable of infecting the atrophic cuboidal epithelium of the prepubertal nonestrogenized vagina.[48] Young children may acquire chlamydia by passing through an infected birth canal or by sexual abuse. In newborns, chlamydia may infect the conjunctiva, pharynx, vagina, or anus. It is estimated that 50%–75% of newborns become infected if their mothers were infected with chlamydia.[49]

Gonorrhea is the most common sexually transmitted disease in abused children and is not likely in children who are not sexually abused.[48,50] It is important to recognize gonorrhea to prevent sequelae and to recognize the child who is sexually abused. Infants can be contaminated through vaginal secretions in the birth canal colonizing the oropharynx, vagina, and rectum. The infection may remain asymptomatic. However, a white, yellow, or greenish, thick vaginal discharge with odor may be present. Labial erythema, urethral irritation, proctitis, or dysuria may be present.

YEAST INFECTIONS

Other than the cutaneous variety associated with diaper rash, yeast infections are more common in adult females than in prepubertal girls. The alkaline vaginal pH of childhood is hostile to yeast.[48] Most yeast vaginitis is caused by *Candida albicans*. Most often, yeast infections are secondary to predisposing host factors, such as broad-spectrum antibiotic use or depressed cellular immunity.

BACTERIAL VAGINOSIS

Less commonly, vaginal infections can be due to bacteria and are often listed as nonspecific or *Gardnerella* vaginitis. This is now recognized to be caused by a mixed flora, including anaerobic bacteria.

PEDIATRIC HEMATURIA

The presence of blood in the urine is a common clinical entity resulting in referral to pediatric urologists. It is a manifestation of abnormalities localized to the urinary tract from the kidneys to the urethra. Hematuria may be visible grossly or seen only on microscopic examination. Urine dipstick measures the presence of hemoglobin in urine and can be falsely positive for hematuria when hemoglobinuria and myoglobinuria are present. Verification of a positive urine dipstick for blood using microscopy can be performed to identify red blood cells (RBCs) within the specimen. To be considered significant for hematuria, UA requires five RBCs per high-power field. RBC casts, dysmorphic or fragmented RBCs, and RBC blebs on UA signify a glomerular source for hematuria. Gross hematuria accounted for an estimated 1–2 patient visits per 1000 in pediatric emergency clinics.[51,52] The incidence of microscopic hematuria in asymptomatic children ranges from 14 to 41 per 1000 individuals when a minimum of four urine specimens was collected.[53,54]

The evaluation of a child with hematuria should be guided in a systematic fashion as determined by history, physical exam, and laboratory tests. Questions regarding the timing of hematuria relative to gastrointestinal, cutaneous, and respiratory infections are important. The presence of UTI symptoms, including dysuria, flank pain, fevers, chills, frequency, and urgency, and a history of recent trauma or prolonged or vigorous exercise add direction to the initial assessment. The character of blood in urine (terminal vs. throughout voiding), passage of clots, and signs of stone passage, including flank pain, nausea, vomiting, and radiating pain, associated with hematuria should be recorded. Documentation of any family history of renal failure, deafness, sickle cell traits or disease, and recurrent hematuria should clue the clinician to a hereditary source of hematuria. Medications, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and certain chemotherapeutic drugs, can be causative in the development of hematuria.

Physical exam should identify the presence or absence of flank or abdominal tenderness, extremity edema, pharyngitis, cutaneous rashes, deafness, fever, and hypertension. Urinalyses demonstrating proteinuria and/or abnormalities of RBC morphology are present in diseases involving the glomerulus or its basement membrane. Nitrites, leukocyte esterase, white blood cells (WBCs), and bacteria should prompt urine culture to tailor antibiotic treatment. Further laboratory and radiographic testing should be based on clinical suspicion.

Asymptomatic microscopic hematuria is often identified when routine screening urine dipsticks are obtained in children. The absence of an inciting event (i.e., trauma),

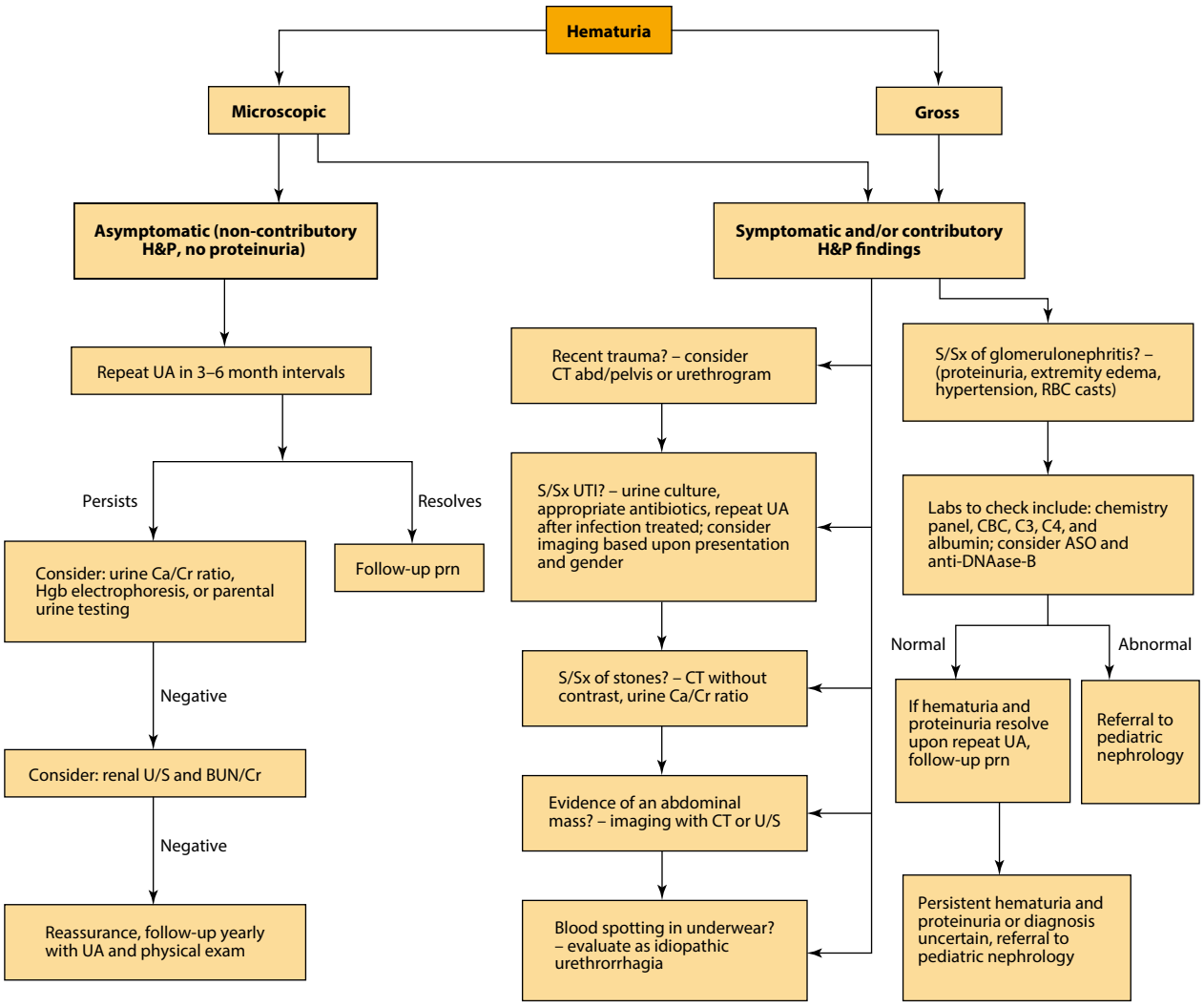

FIGURE 10.13 Diagnostics algorithm for pediatric hematuria. For abbreviations see text. In addition: BUN, blood urea nitrogen; S/Sx, signs and symptoms; prn, as required; H&P, history and physical examination; Hgb, hemoglobin.

proteinuria, infection, hypertension, lower extremity edema, and renal insufficiency is reassuring, and most of these patients can be observed with follow-up UA in 3- to 6-month intervals until they normalize. When attributable to vigorous exercise or medications (i.e., NSAIDs), repeat UA can be performed every 1–2 weeks after discontinuation of the offending source, to confirm resolution of the hematuria. Diagnostic tests, such as radiographic examinations (U/S or VCUG), or invasive procedures, including renal biopsy or cystoscopy, are not warranted in these patients.[55] If asymptomatic gross hematuria or persistent microscopic hematuria occurs, diagnostics testing can be tailored based on history and physical examination.

When persistent microscopic hematuria develops without a contributory history or physical examination, obtain the calcium/creatinine (Ca/Cr) ratio, parental UA, and hemoglobin electrophoresis (if the patient is of African American descent), to assess for hypercalciuria, benign familial hematuria, and sickle cell disease or traits, respectively. The spot Ca/Cr ratio is considered abnormal when greater than 0.21 in children older than 6 years of age.[56] Alternatively, a 24-hour urine collection demonstrating a urine calcium level greater than 4 mg/kg/day is diagnostic for hypercalciuria.[57] In a small retrospective study of children referred for microscopic hematuria,[55] evaluation of serum electrolytes, creatinine, cystoscopy, VCUGs, and U/S of the kidneys and bladder failed to show abnormalities. However, serum creatinine and renal U/S are often utilized to assist in the initial evaluation despite their apparent low yield. When normal, parents can be reassured that their child's prognosis is excellent. Nonetheless, these patients should be followed yearly to assess for the development of proteinuria, hypertension, or new symptoms, or the resolution of hematuria that would alter current management.

When microscopic hematuria is associated with symptoms, patient evaluation should be tailored based on clinical presentation. The concomitant presence of proteinuria, hypertension, and peripheral edema should prompt an assessment to distinguish between glomerular etiologies of hematuria. Laboratory tests, including a chemistry panel, complete blood cell count (CBC), C3, C4, albumin, anti-streptolysin-O, and anti-DNAase-B antibodies, will

facilitate discriminating between the different immune and basement membrane abnormalities. Prompt referral to a pediatric nephrologist should occur in the presence of an acutely ill child, rapidly progressing or chronic glomerulonephritis, patients exhibiting symptoms of nephritic syndrome, uncertainty of a correct diagnosis, or the need of assistance in management and therapy.[58] However, when microscopic hematuria is associated with a small amount of proteinuria, a conservative course with close follow-up can be instituted with further investigation utilizing the above algorithm if evidence of persistence or clinical progression occurs.

If a history of recent trauma is present, computed tomograms (CTs) and retrograde urethrograms are warranted based on the clinical scenario and judgment. When signs or symptoms worrisome for a UTI are present, protocols should include obtaining urine cultures, instituting antibiotic therapy based on culture sensitivities, and repeating a formal UA and culture after the infection has been treated to assess for resolution of the hematuria. Noncontrast CT and urine calcium analysis are helpful if urolithiasis is suspected, and abdominal imaging (U/S or CT) if an abdominal mass is palpated.

The presence of gross hematuria can be differentiated based on its appearance. Tea- or cola-colored urine suggests a glomerular source. Bright red urine with normal morphology on microscopic examination suggests a urothelial etiology for the hematuria.[59] The absence of RBCs on microscopic examination in light of a positive dipstick may be indicative of hemoglobinuria or myoglobinuria. Subsequent workup for gross hematuria is driven primarily by clinical presentation. Signs and symptoms suggestive of stones, infection, recent trauma, or glomerulonephropathies can follow protocols similar to those described for symptomatic microscopic hematuria.

Idiopathic urethrorrhagia is seen in prepubertal boys who present with blood spotting in the underwear between voiding. In a review at our institution, dysuria was reported in ~30% of patients and the mean age at presentation was 10.1 years old.[60] Laboratory and radiographic studies—intravenous pyelography (IVP), U/S, and VCUG—are routinely normal, although RBCs can be seen in up to 57% of patients.[60,61] Symptoms can persist, ranging from a few weeks to 3–4 years. Etiology is unknown, although anterior and posterior urethritis has been documented.[60,62] Cystoscopy is generally considered unnecessary unless symptoms persist greater than 24 months, as urethral stricture may be identified. This process is self-limited and resolves by puberty without treatment.

For a review of the diagnostic algorithms presented for pediatric hematuria, refer to Figure 10.13.

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CHAPTER 11

Principles of Minimally Invasive Surgery

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INTRODUCTION

Laparoscopy is now a popular surgical approach in pediatric urology, reducing the invasiveness of treatment and shortening the period of convalescence. At present time, with the development of new instruments better designed for pediatrics, laparoscopy in all ages may be a safe and effective way to treat a variety of urologic disorders. Since pediatric urologists lack the luxury of being exposed to common and frequent surgical procedures aside from pyeloplasty and nephrectomy, it is natural that the learning curve is steep. Hence, in order to master this surgical modality and technique, the novice must acquire a set of basic knowledge in pediatric physiology pertaining to laparoscopic surgery, and be adept to current and fast-evolving technology, while being exposed to a large number of cases where the laparoscopic approach may be incorporated.

Prior to any surgical procedure, a brief description of the surgical approach and patient positioning, in addition to a list of the needed instruments during the surgery, should be gone over with the operative team, nurses, and anesthesiologists. In addition, the surgeon should become familiar with the available laparoscopic instruments and comfortable with troubleshooting the tower, insufflation, and other common issues that may occur during laparoscopic procedures.

PATIENT SELECTION AND PREOPERATIVE EVALUATION

The majority of children are good candidates for minimally invasive intervention, either laparoscopy or robotic procedures. There are, however, relative contraindications, such as poor cardiopulmonary reserve and impaired CO_2 exchange, as well as absolute contraindications, such as intra-abdominal infection, that would prohibit insufflation of the abdomen.

Other relative contraindications that are dependent on the dexterity of the surgeon are bowel adhesions and previous abdominal surgery, in addition to peritoneal dialysis. A history of previous abdominal surgery can sometimes be circumvented with adequate visualization and meticulous dissection. Finally, a relative contraindication is bleeding diathesis.

Preoperative testing in infants should include a prothrombin time (PT), partial thromboplastin time (PTT), hemoglobin, hematocrit, and creatinine, with urine culture, especially if there is a bladder or urinary system intervention to be performed. Similar recommendations, such as hematology or cardiology or pulmonary consults, are only recommended if the patient has a history of bleeding tendency or cardiac or pulmonary disease. Traditionally, most of the children that undergo routine laparoscopy procedures, such as nephrectomy or pyeloplasty, would benefit from a baseline hemoglobin or hematocrit, although many would consider this unnecessary in the healthy child.

PEDIATRIC PHYSIOLOGIC CHANGES

Anesthesia

Induction and maintenance of anesthesia may be achieved with either inhalational or intravenous agents or a combination of both. Nitrous gas increases bowel distention, potentially bringing the peritoneum closer to the area of dissection for retroperitoneal procedures and furthermore decreasing the working space in transperitoneal procedures.

Like any surgical procedures, intraoperative monitoring should include a routine electrocardiogram (ECG), noninvasive blood pressure, SpO_2, temperature, and inspired oxygen concentration. Although end-tidal CO_2 may not accurately reflect arterial CO_2 tension, its use is helpful in planning appropriate ventilation strategies in case pulmonary decompensation occurs after CO_2 insufflation. In infants and children with respiratory illness, capillary or arterial blood gas analysis might be needed to accurately monitor CO_2 tension.[1] Maintenance of intravenous fluid is usually sufficient unless there is unanticipated bleeding, keeping in mind that urine output is usually low during insufflation and does not reflect dehydration.[2]

Anesthesia and Positioning

Although positioning is intended to facilitate surgery and improve the ergonomics of the surgical team, it is evident that pediatric patients not only have a small intracorporeal space, but also may have a limited extracorporeal space. This restrictive landscape makes it necessary for the surgeon and anesthesiologist to share the space in case an emergency situation erupts. For instance, when patients are placed in flank positions, insertion of the intravenous line in the arm on the side of the surgery allows for easy access.

Furthermore, patient positioning during laparoscopic surgery may potentiate the impact of gas insufflation. For instance, the Trendelenburg position during laparoscopy will increase the heart rate and vascular resistance while decreasing mean arterial pressure and cardiac output, whereas the opposite effect is seen in the reverse Trendelenburg position. Furthermore, flank positioning, especially with the kidney rest up and the patient flexed, will accentuate impaired venous return and increase cardiac strain. In fact, the left lateral decubitus position produces more significant hemodynamic and respiratory changes than the right flank position.[3]

CO_2 and Pressure Effects

As gas is placed in a closed space, it moves depending on the partial pressure gradients. Once the pressure rises, a plethora of cardiovascular, pulmonary, and renal effects may be seen (Video 11.1a,b). The heart rate and mean arterial pressure increase while the venous return and cardiac output decrease. These parameters are seen even when pressure is set at a standard working level of 10–15 mmHg. Above this level, more profound hemodynamic alterations are anticipated to occur, with a further decrease in cardiac output. Furthermore, limitation of diaphragmatic mobility may cause respiratory restriction manifested by increased airway pressure, requiring an increase in the peak end-inspiratory pressure to maintain a set tidal volume. Finally, renal effects occur secondary to gas insufflation, manifested by decreased glomerular filtration rate (GFR) and urine output. Animal studies have shown that gas insufflation causes renal vein compression, including decreased renal blood flow, decreased urine output, and diminished creatinine clearance. Although these effects do not cause renal damage in humans,[2] it is crucial and important information that the operating surgeons know about.

Traditionally, in the pediatric population the insufflation rate should be based on the age or weight of the patient. In patients that are younger than 1 year of age, we usually use a 0.3 L/min flow; while in patients between 1 and 5 years of age, we use 0.5 L/min. In patients between the age of 5 and 10 years, we use 1 L/min flow, and for patients older than 10 years, we usually use 2 L/min. With the onset of insufflation, surgeons and assistants need to be competent to address any of the possible complications that may occur, such as CO_2 embolism or pneumothorax. CO_2 embolism is manifested by right heart failure, whereas pneumothorax is manifested by an acute drop in oxygen saturation.

Absorption Effects

Although the absorption of the insufflated CO_2 into the blood is limited, its diffusion is determined by many variables; most important are the pressure differential and the cross-sectional area of the absorbing surface. Both the peritoneal and retroperitoneal spaces are closed yet expansible. The physiologic consequences of CO_2 insufflation may be related to the compressive effects of the gas or the metabolic consequences of the gas absorption. With insufflation, the gas will attempt to reach equilibrium with the surrounding environment; such equilibrium is controlled with the use of insufflators that not only control the flow of gas but also monitor the feedback pressure generated from the insufflation.

The effects of gas absorption are either pulmonary or hemodynamic. The pulmonary effects are increased CO_2 retention and increased end-tidal CO_2, exacerbated by decreased functional residual capacity and decreased diaphragmatic excursion. The hemodynamic effects of hypercarbia are increased heart rate, vasodilation, and increased cardiac contractility. Although in healthy children there is little, if any, added cardiorespiratory risk from laparoscopic procedures, children with cardiopulmonary compromise require close and careful monitoring.

INSTRUMENTATION

Rapid progress in video technology and the miniaturization of instruments to <3 mm in diameter have made the performance of a variety of pediatric laparoscopic procedures possible. Instruments of this size and larger come in nearly every variety (scissors, needle holders, dissectors, graspers, clamps, suction devices, energy delivery devices, etc.) and facilitate the performance of the most complex cases. Nevertheless, the surgical procedure, in combination with the size of the patient, will determine the surgeon's selection of instruments and telescope size. Laparoscopic trocars are available in 3, 5, and 10 mm sizes, with varying degrees for optimal visualization. For most ablative or reconstructive urologic procedures, 3 or 5 mm trocars are sufficient. However, sometimes 10–12 mm trocars may be necessary if a stapling device needs to be utilized, or when specimen extraction is anticipated.

ACCESS

Traditional Laparoscopy

There are two techniques to gain access into the peritoneum: blind access and access through visualization, often referred to as closed versus open access. The blind closed approach is facilitated through the use of the Veress insufflation needle. A stab wound is made, either in the middle of the umbilicus or just below typically, with either a #15 or a #11 blade. The Veress needle is inserted through the 1 mm opening and passed through all layers of tissue, and verification of placement is confirmed by opening the stopcock and infusing a small amount of saline. For transperitoneal procedures, it may be more accurate to attach the insufflation needle to the insufflator and monitor pressures. Low pressures (<10 mmHg) are a reliable indication of being intraperitoneal. The second technique is the open (Hasson) approach, and this approach may be facilitated through the use of direct and telescopic visualization of all tissue during insertion of the trocar with a blunt obturator. This technique has been generally preferred in children and is especially ideal in obese patients. Another currently preferred technique by many surgeons because it is fast, safe, and accurate is the Bailez incision at the umbilicus

combined with a radially dilating trocar.[4] Placement of accessory ports should be carried out using direct vision from within. The location of the accessory trocars depends on the operation to be performed, and specifics of all trocar placements are described below in the transperitoneal and retroperitoneal laparoscopy subsections of this chapter. All proposed trocar sites are injected with 0.5% bupivacaine, with 1:100,000 epinephrine after insufflation and prior to accessory trocar placement. The purpose of this step is to decrease the postoperative pain and further provide an accurate location of the trocar position, hence avoiding finger pressure in children with a small peritoneal cavity and obscuring the accurate trocar location.

Trocar Fixation

Once the primary trocar is introduced and prior to CO_2 insufflation, a 2-0 Vicryl (UR-6 needle) suture may be placed around the trocar and in the fascia as a purse-string suture (Video 11.2). After the depth of the trocar is well delineated, this suture is tied to the side of the port and serves several purposes: it prevents the trocar from moving in or out during instrument manipulation, it decreases the possibility of subcutaneous emphysema or leakage of CO_2 from around the trocar site, and it can be used to lift the abdominal wall to enlarge the retroperitoneal space.

For the accessory trocars, a short (~1 cm) section of rubber, plastic tubing, or cone can be placed around the trocar shaft, about one-third of the way from the tip to the hub of the trocar. This prevents the trocar from being pushed into the surgical cavity as instruments are advanced. This surgical step is rarely needed, especially if the accessory trocars are inserted through a small stab incision—hence the tight entry site.

Insufflation

Newer insufflators can deliver a great volume of gas rapidly; this may be dangerous in an infant weighing less than 2 kg. In addition to pressure fluctuation, CO_2 insufflation with unwarmed high-flow gas may cool a tiny infant quickly. Whereas the rule is to insufflate with just enough pressure to have unobstructed visualization, pressures of 15 mmHg appear to be well tolerated in any size patient, with the only issue being ventilator compromise in infants with marginal lung function. For all laparoscopic procedures, CO_2 insufflation should be started at a pressure of 12–15 mmHg for children of >2 years old and 8–10 mmHg for children of <2 years old.

Robotics

Today's surgical robots, or what the true enthusiasts call "surgical actuators," allow freedom in the operating room that we only imagined not too long ago. Over the past decade, there have been a series of surgical manipulators, which receive digital instructions from an interfaced computer. Unlike industrial robots, they are not autonomous. Their birth was a reflection of the growth in minimally invasive surgery (MIS), mainly laparoscopy. Laparoscopy, although excellent for extirpative surgery, is a challenging medium for reconstructive surgery in all but the most experienced hands. Minimally invasive laparoscopic surgery has two severe limitations for those who cannot afford to spend the time in specialized training for MIS: (1) only four degrees of freedom, which makes intracorporeal suturing and tying a complicated task, and (2) a lack of three-dimensional visualization. The current industry-supported robotic platform, the da Vinci Surgical System (Intuitive Surgical, Sunnyvale, California), provides the advantages of delicate manipulation for reconstructive surgery combined with three-dimensional visualization (if the largest lens is used). This current robotic platform entails a surgeon seated at an ergonomically designed video console with an "immersive" three-dimensional display. The surgeon initiates the digital instructions by controlling finger grips giving seven degrees of freedom by adding the pitch, the yaw, and a pincer movement to those already existing in MIS. The manipulators inside the patient's body duplicate the surgeon's hand movements at the console, and software carries the capability of filtering out hand tremors.

Robotics can be helpful for manipulation in hard-to-reach places. In urology, radical prostatectomy is performed in a challenging environment: under the pubis in the confined space of the pelvis with limited visualization and movement. The most difficult surgery in regards to open access in adults always seems to be deep in the pelvis. So it is not surprising that robot-assisted prostatectomy is continuing to grow in the United States. The surgeon is not optimized for tight spaces, but the robot is.

Robotic surgery will allow surgeons to perform more complex minimally invasive procedures that may be too tedious and time-consuming with standard laparoscopy. Intracorporeal suturing is a rate-limiting step in pure laparoscopy, and mastery of this technique is time demanding. Robotics allows this step to be facilitated. The robotic software can scale down a surgeon's hand movements into "micromotions," virtually eliminating tremor and allowing the surgeon to be even more precise and accurate than laparoscopic and possibly even open surgery.

The lack of tactile feedback has skeptics concerned. If one takes a step back, one would realize that when we manipulate tissue and the small sutures during pediatric surgery, there is less reliance on tactile feedback. It is mostly done by visual cues. Nonetheless, tactile feedback is currently under investigation, and its addition to the current robotic platform should enhance the performance.

Despite its early success, robotic surgery still poses many challenges in pediatric patients. As in laparoscopic surgery, the small working distance on the abdominal wall in a child can significantly limit the mobility of the robotic instruments. In such a small operative field, a difference of a few millimeters can greatly affect the safety of the operation. The location and placement of the robotic trocars is critical in children and typically requires slight variations compared with placement in adults. Because of the diminished thickness of the abdominal wall, mostly in the infant population, keeping the trocars in place with desufflation during instrument exchange remains a challenge. One technique that might be useful is anchoring the abdominal wall to the trocar with a heavy suture in order to keep the abdominal wall in place if rapid desufflation should occur. The trocars cannot be as deep in the pediatric abdomen as they would be placed in the adults.

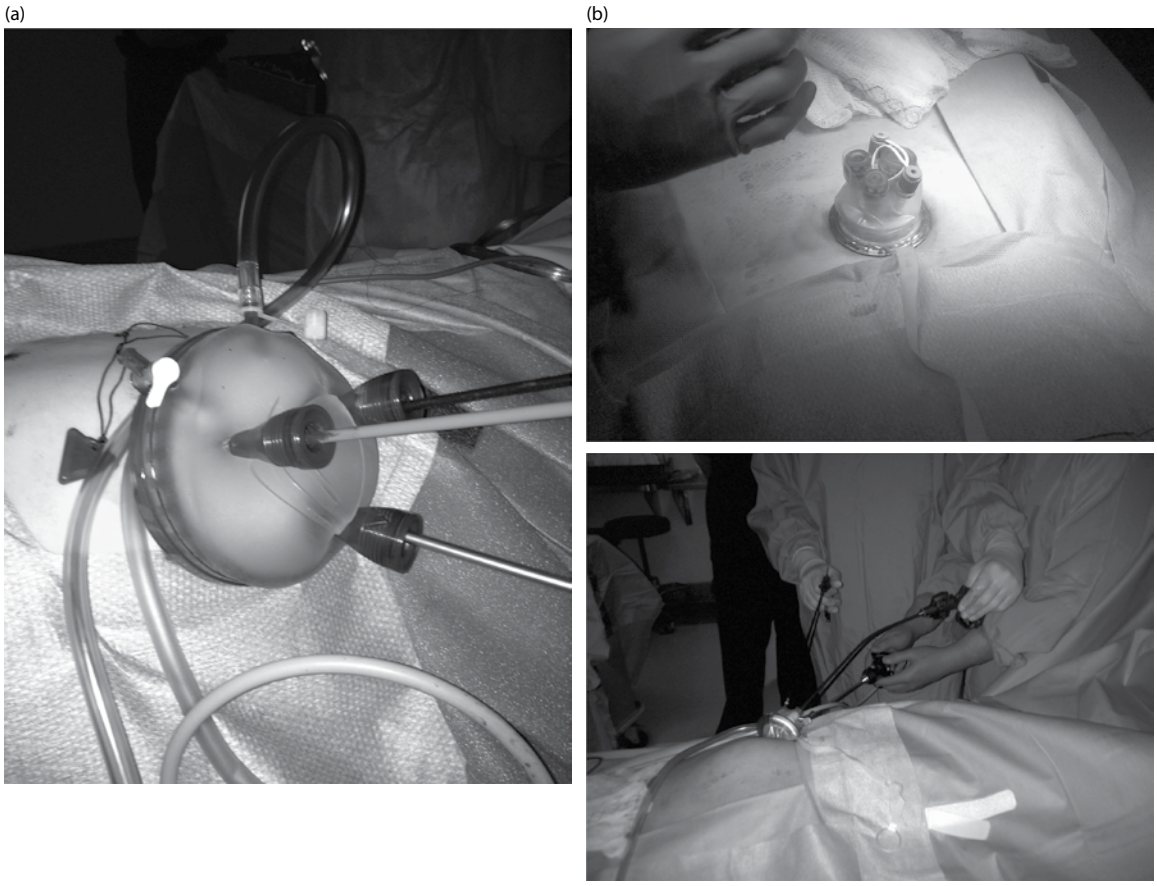

FIGURE 11.1 (a) GelPOINT apparatus in situ. The benefits of this instrument are the triangulation and the ease of use of traditional instruments. (b) Triport (Olympus) is one of the available single-port accesses to perform LESS. Due to the proximity of the ports, specific instruments are usually recommended to be used with this port.

The current surgical robotic platform offers both 12 and 8.5 mm and 0° and 30° telescopes that offer three-dimensional imaging. There is a 5 mm endoscope available, but it is monocular and cannot provide the three-dimensional image of the larger scope. The working ports come in 8 and 5 mm trocars. The robotic device is docked from the ipsilateral side in the upper urinary tract surgery or the foot of the bed in the lower urinary tract surgery and orchiopexy, and the robotic arms are engaged. The robot has instruments that are available in both 8 and 5 mm sizes that complement traditional laparoscopic instrumentation, with a slight paucity of instruments in the 5 mm category. A fourth arm is available for grasping and retraction, but in the small pediatric patient, this arm has limited use.

Laparoendoscopic Single-Site Surgery

Although laparoendoscopic single-site surgery (LESS) is feasible in children, its role, cost-effectiveness, and outcome in comparison with traditional laparoscopy have not been established. Initially, LESS procedures primarily used existing laparoscopic and endoscopic equipment to perform simple procedures, such orchiopexies or varicocelectomies.[5] But the development of improved laparoscopic cameras, as well as articulating instruments, helped to overcome coaxial limitations and "sword fighting" of instruments. The EndoEye™ (Olympus), for example, is a 5 mm scope that has a digital chip at the deflectable tip that provides a wider field of view. This advanced technology, coupled with articulating instruments, allowed the use of this approach in a variety of procedures, including nephrectomy and pyeloplasty.[6]

Currently, LESS is performed using multiport divides, which is a multiple-instrument access port. This port usually will accommodate a scope and two or three additional instruments. There are a variety of access devices available on the market and produced by several manufacturers, for a variety of procedures (Figure 11.1). In children, the traditional location of the single incision used for procedures is the umbilicus (Video 11.3a,b). The umbilical incisions for LESS are usually scarless and may be particularly well suited to procedures such as nephrectomy or pyeloplasty (Figure 11.2).[7]

OPERATIVE APPROACHES

Retroperitoneal Approach

Indications for Retroperitoneal or Transperitoneal Laparoscopy

- Total nephrectomy.
- Partial nephrectomy for duplicated renal system.

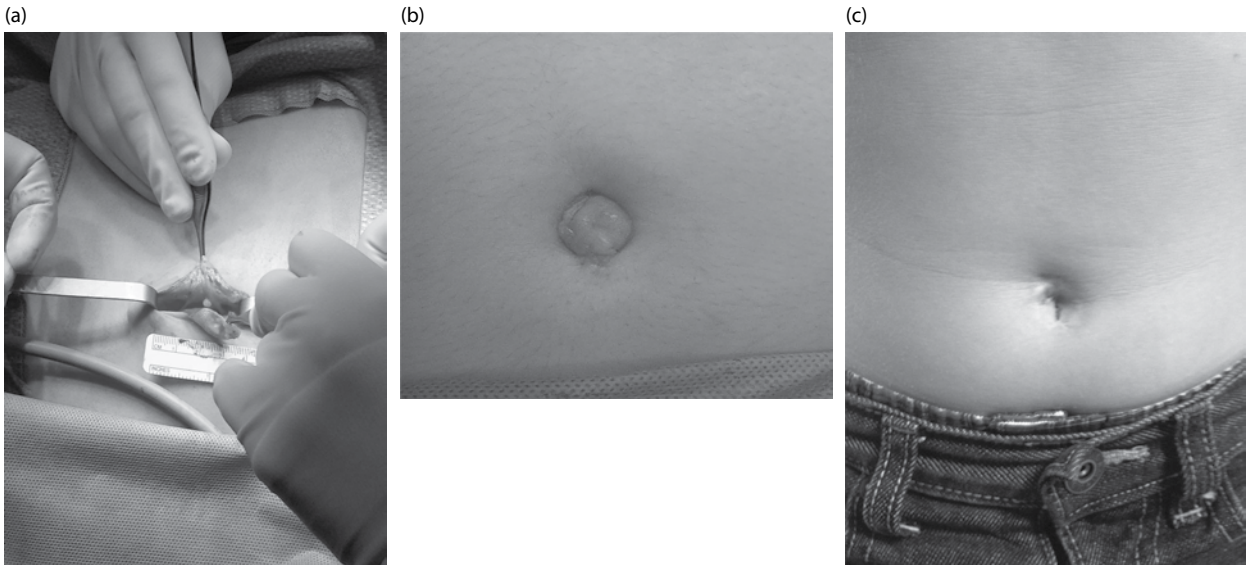

FIGURE 11.2 An umbilical incision is the current approach for LESS in children. A skin incision (a) is performed on the protruding umbilicus, and then with adequate retraction, a generous fascial incision to accommodate the single port is made. Immediate postoperative view (b) of the umbilical incision and a few months later on follow-up (c).

- Distal ureterectomy for duplication anomaly.
- Pyeloplasty.
- Pyelolithotomy and ureterolithotomy. Extracorporeal lithotripsy and endourologic procedures have almost eliminated the need for open surgery to remove urinary stones. On the other hand, in patients who have unusual anatomy, such as ectopic kidneys, a laparoscopic approach may be used either to perform pyelolithotomy or to help in getting direct percutaneous access to the kidney.
- Adrenalectomy for cortical adenoma associated with congenital adrenal hyperplasia.

Contraindications to Laparoscopy

Contraindications to laparoscopy in infants, children, and adolescents are the same as for any other surgical procedure, except for evidence of limited lung reserve function, which may be considered a relative contraindication. If the patient is septic, in shock, or exhibits a coagulopathy, these should be corrected before surgery is contemplated. If surgery is deemed essential under these circumstances, then it probably should be performed open.

Strong contraindications:

- Cardiopulmonary morbidity.
- Uncorrected coagulopathy.
- Sepsis.
- Malignant tumors. Although laparoscopy may play a role in the staging of malignant pediatric abdominal tumors, such as Wilms' tumor or neuroblastoma, its role in the management of these tumors has yet to be defined. Morcellation of specimens for extraction has raised concerns about accurate pathologic staging; hence, large-sized tumors mandate an incision to retrieve them. In addition, the fragile consistency of the tumor makes it more prone to rupture, and hence may obviate the use of this technique.

Retroperitoneal Laparoscopic Approach

Relative contraindications:

- Prior retroperitoneal scar (kidney surgery, kidney biopsy, or pyeloplasty)
- Previous infectious or inflammatory retroperitoneal process (xanthogranulomatous pyelonephritis), except for experienced surgeons in this approach

Advantages:

- The technique mimics the open urologic surgical procedure through the retroperitoneal approach.
- This direct approach to the organs of the genitourinary tract requires less dissection to the colon or the spleen to expose the kidneys and adrenals.
- Previous transperitoneal surgery does not preclude retroperitoneoscopy.
- Trocar sites have less postoperative hernias than an open incision.
- It facilitates the view of the posterior surface of the kidney, and hence rapid access to the renal hilum.

Disadvantages:

- Manipulation of instruments may be initially difficult due to a restricted working space; e.g., in reconstructive surgery such as pyeloplasty, suturing and knot tying may be difficult, and in ablative surgery, the degree of technical difficulty increases in the presence of large-sized specimens.
- Achieving anatomic orientation may initially be a challenge for the inexperienced laparoscopist.

Patient Preparation and Positioning

Bowel preparation for retroperitoneoscopic renal surgery in children is not recommended. Although the

retroperitoneal approach may be accomplished with the patient prone,[8] we prefer the flank position, as it increases the anteroposterior dimensions of the retroperitoneal space and is a suitable position in cases where we need to convert to transperitoneal or open approaches. The patient is positioned in the full 90° flank position as close to the posterior edge of the table as possible. To further increase the retroperitoneal space, the table is flexed and the kidney rest elevated. Pressure points are padded and an axillary roll is placed to prevent postoperative complications, such as brachial plexus palsy. The patient should be taped to the table using 3-inch adhesive tape placed across the shoulder and the hips so that the patient will remain secured while the table is moved during the surgery.

We prefer to have the surgeon and assistant standing on the same side of the table, and we use only one monitor. We believe that having both the surgeon and the assistant in the same line of vision facilitates eye–hand coordination, particularly that of the assistant surgeon.

Anatomic Considerations for Retroperitoneal Laparoscopy

An understanding of the retroperitoneal surgical anatomy is mandatory before embarking on retroperitoneal surgery. The boundaries of the retroperitoneal space are

- Posteriorly and laterally—the paraspinous, psoas, and quandratus lumborum muscles, which are anatomically fixed structures
- Anteriorly—the mobile posterior parietal peritoneum and its contents
- Superiorly—the diaphragm
- Inferiorly—contiguous with the extraperitoneal portions of the pelvis

The retroperitoneum contains the great vessels, kidneys, adrenals, and ureters, in addition to the perirenal adipose and areolar tissues. Since there is no preformed space, pneumoretroperitoneum is only accomplished after breaking up the adipose areolar tissue in the retroperitoneum.

Laparoscopic Technique

Access to the retroperitoneum is preferably achieved by the open (Hasson) technique, which provides visual guidance (Video 11.4a,b). As children have a small retroperitoneal space, and close proximity between the abdominal wall and the major vessels, the closed technique is not recommended. In addition, since there is no actual preexisting retroperitoneal space, the placement of a Veress needle is not precise and may cause injury to either the great vessels or pneumoperitoneum.

In the midaxillary line, a 1 cm long incision is made 1–2 cm below the tip of the 12th rib. The muscles are split in the direction of their fibers, and then the lumbodorsal fascia is incised to enter the retroperitoneum. The method of the development of the retroperitoneal space using a blunt instrument or the balloon dissector is up to the surgeon. Although commercial balloon dissectors are readily available, an inexpensive balloon can be made using the finger of a surgeon's glove tied around a catheter. The balloon is inserted anterior to the psoas muscle and outside Gerota's fascia, and approximately 400–500 mL of air is used to inflate the balloon, creating the space. Instead of using a balloon, we introduce a wet gauze close to the posterior muscular wall to create the retroperitoneal space.

Insertion of the primary trocar in the correct space is of paramount importance because inserting the trocar too far medially may result in peritoneal entry or colon injury, whereas entering posteriorly in the quadratus or psoas muscle may cause bleeding. If Gerota's fascia is easily visible, it is incised and opened for direct CO_2 insufflation, although this technique may be associated with inadvertent peritoneotomy. For this reason, it is preferable to create the retroperitoneal space outside Gerota's fascia, dissect the peritoneum medially, insert the posterior secondary 5 mm trocar, open Gerota's fascia under vision, and proceed with the creation of the retroperitoneal space by medially dissecting the peritoneal reflection for the third trocar insertion.

We exclusively create the retroperitoneal space using blunt dissection, using a wet sponge that is inserted in the retroperitoneal space and advanced inferiorly toward the pelvis and superiorly. In very small children, the sponge may need to be cut in half. Through the incision and with the psoas muscle as a reference point, a 10 mm trocar with the laparoscope (0°) is inserted to confirm correct placement. Initially, the posterior inferior aspect of Gerota's fascia and the lower pole are visualized. Identification of the psoas muscle posteriorly is crucial; on the other hand, anteriorly, the edge of the peritoneum is identified and swept medially to expose the underside of the tranversalis fascia. To avoid tearing the peritoneum, it is dissected medially by manipulating the laparoscope in a lateral to medial fashion close to the abdominal wall to expose the internal surface of the transversalis muscle. Having created the working space, two 5 mm secondary trocars are inserted. The posterior secondary port is inserted approximately midway between the 12th rib and the iliac bone, and lateral to the border of the paraspinous muscles. Using a grasper through this trocar, the peritoneum is further mobilized to create the pelvic extraperitoneal space. The anterior secondary trocar is inserted at the anterior axillary line 2 cm superior to the iliac crest. Although the space may be limiting, the two secondary ports should be inserted as far apart as possible to improve ergonomics.

In order to place the secondary trocars under vision, a 30° laparoscope may be used. However, we use the 0° telescope, and we insert the trocars in the following fashion for both the retroperitoneal and the transperitoneal approach. A small skin stab is made using a #11 blade, after anesthetic is injected. Through the stab incision, a straight clamp is advanced and the fascia is stretched; then using sharp-tipped obturators, the trocars are advanced through the muscles and fascia. Once in the retroperitoneal space, a blunt-tipped obturator is exchanged for a sharp one and the trocars are advanced into the retroperitoneum. This safety tip prevents injury to the peritoneum or the major vessels. In addition, while inserting the trocar, it should be directed toward the area of dissection because if the trocar is advanced away from the site of dissection, this might result in constant tension on the skin during surgery or a greater chance of gas leakage at the trocar site.

Although the sites of the telescope and other trocars are the same for all retroperitoneal renal and adrenal laparoscopic procedures, the sequence of operative strategy and the need for accessory trocars depend on the surgical procedure. In the event that more than three ports are required, laparoscopic guidance and bimanual palpation are recommended for accurate placement. For instance, during retroperitoneoscopic pyeloplasty, an additional port may be required to maintain traction on the ureteropelvic junction for better exposure; in this case, a fourth trocar (3 or 5 mm) is placed along the anterior axillary line at the tip of the 11th rib. In order to avoid inadvertent peritoneotomy, adequate dissection of the peritoneal reflection medially at the trocar insertion point is mandatory.

The following laparoscopic landmarks are useful for orientation in any retroperitoneoscopic renal procedure: the psoas muscle and posterior aspect of the kidney are identified first. This approach allows rapid visualization of the "vertically" oriented main artery and vein. To further facilitate exposure of the renal pedicle, save dissection of the anterior surface of the kidney to the last step. This will maintain retraction on the renal pedicle in case a nephrectomy or a partial nephrectomy is contemplated. In addition, this approach will suspend the kidney anteriorly, exposing the ureteropelvic junction in case a pyeloplasty is performed.

For identifying the renal hilum, we first locate the psoas muscle, and then find the great vessels medially, the aorta, or the vena cava; this may help to locate the renal hilum. On the right-hand side, initial identification of the inferior vena cava on the medial aspect of the psoas muscle facilitates identification of the gonadal, renal, and possibly suprarenal veins, which are located in the same plane. On the left-hand side, the pulsations of the aorta are often visualized and help guide the surgeon to the renal artery.

Transperitoneal Laparoscopic Approach

Transperitoneal procedures provide exceptional exposure since the intraperitoneal space is large.

Patient Preparation and Positioning

For upper transperitoneal procedures, positioning the patient in a flank or modified flank position at the edge of the table is crucial. This positioning allows the surgeon full access to the abdominal cavity without limitations caused by the edge of the table. For the modified flank, a roll should be placed under the torso to provide a 60° patient angulation from the table. The patient should be secured, so that the table may be repositioned as necessary during the procedure. The main monitor should be placed on the lesion side of the operative table, with a slave monitor behind the surgeon. All cables, lines, and wires for the instruments should preferably go off the opposite side to the surgeon. This positioning and port placement is used for the majority of renal interventions, such as nephrectomy, hemine-phrectomy, pyeloplasty, and other renal extirpative and reconstructive procedures. The transabdominal approach also allows access to the pelvis by altering the port use via placing the camera through the subcostal port and instruments through the umbilical and lateral ports.

For lower transperitoneal procedures in infants, it is most convenient to position the patient at the foot of the bed, across the bottom, and to stand at the side of the bed (at the patient's head) to operate. This is a good approach to the bladder. For older patients, a midtable, supine position with a sacral roll to thrust the pelvis up is preferable. Usually, the side opposite the lesion is chosen, and the telescope placed centrally in or near the umbilicus. The instrument trocars are placed lateral to the rectus muscle after insufflation, sufficiently superior and inferior to the telescope cannula so that the instruments can be introduced at a 45° angle relative to the operative field. The monitor should be located toward the foot end of the operative table. Only one monitor is necessary in this scenario. All cables, lines, and wires should be off the foot of the bed for optimal ergonomics.

This approach is extremely helpful for gynecologic and urologic procedures in the pelvis, including transvesical approaches. The new transvesical procedures, such as ureteral reimplantation, require cannula fixation so that the bladder mucosa does not strip and dissect away from the detrusor muscle. One way to achieve this is to perform a cystosomy at the skin incision to help hold the bladder wall and mucosa to the anterior abdominal wall. A balloon-tipped cannula may also be helpful here, but the size of the balloon tip may impair instrument manipulation in a small child.

Laparoscopic Technique

Transabdominal access is best achieved through the umbilicus using the open technique previously discussed, whereby the umbilical scar is lifted using an Allis clamp; then, using a #11 blade, the skin and subcutaneous tissue are incised and the peritoneum is entered.

Instruments can be placed directly through a stab wound without the need for a trocar if the surgeon does not anticipate repeatedly withdrawing and reinserting instruments through the site.

In infants and thin children, the laxity of the abdominal wall might allow large trocars or heavy instruments to compress the abdominal wall, obscuring vision and limiting CO_2 distention. Once access is attained, sometimes bowel, bladder, or other structures can obstruct the view. It can be helpful to pass one or more sutures through the abdominal wall, through the structure, and back out through the abdominal wall for retraction. These can be tied to a self-retaining retractor or can simply be tied at the distended abdominal wall if that is sufficient.

TECHNICAL LAPAROSCOPIC TIPS

Hemostasis

Vessels may be ligated with laparoscopic clip-applying devices that are available in 5 and 10 mm sizes. Laparoscopic tie-assisting devices are also available if clips are not preferable. They typically require a $\geq$5 mm cannula and either have a cinch knot technology or allow extracorporeal tying and knot placement with a pusher device. Freehand laparoscopic tying can also be performed, but is time-consuming and does not seem to be beneficial with the current hemostatic devices available.

Laparoscopic stapling devices are available for hemostasis. They are an excellent alternative for large vessels and for transecting thick tissue, such as bowel mesentery. The laparoscopic stapling devices require a ≥10 mm trocar for access and come in different lengths, deployment widths, and angulation capabilities. The tissue or vessel is transected as the staples are deployed. One must ensure that the device completely traverses the target before deployment; otherwise, hemorrhage can occur, especially with large vessels or thick vascular tissue. Stapling devices have been routinely utilized for main organ vessels, as well as mesentery, with reproducible success. If dividing vascular structures, one must be certain that the device contains vascular and not gastrointestinal staples.

There are three basic energy sources for hemostasis: monopolar, bipolar, and ultrasonic. The main difference between monopolar and bipolar modalities is that in monopolar surgery, the current goes through the patient to complete the current cycle, while in bipolar surgery, the current only goes through the tissue between the two electrodes of the instrument.

In monopolar surgery, electrical current created in the source unit passes through a single electrode to the tissue, causing the desired tissue effect almost exclusively near the electrode, since the density of electrons diminishes rapidly as the distance from the electrode increases.

To complete the cycle, however, the current needs to exit the patient, and will invariably choose the path of least resistance in seeking to return to an electron reservoir, such as the ground. Currently, most operating rooms use an isolated generator system with a dispersive electrode pad that is attached to the patient in relative proximity to the surgical site. This creates a set path for the current to exit the patient. The large surface area of the dispersion pad results in low current density at the attachment site, thereby minimizing the risk of skin burns. However, if the dispersion pad becomes loose with only partial skin attachment, the current density increases with the potential risk of skin burns. For maximum safety, the pad should be applied to well-perfused, dry, hairless skin over a large muscle and away from bone or metal.

Bipolar electrosurgery is generally performed at low voltage since tissue impedance is relatively low due to the proximity of the two electrodes. For this reason, these instruments are less effective for cutting tissue since adequate vaporization is difficult to achieve. The current travels from one electrode to another in a short distance. Typically, only the tissue in between the electrodes is affected by the current of energy. Different companies use bipolar energy with modifications, such as what is termed plasmakinetic, which allows cooling in between bursts of bipolar energy delivery to allow a greater amount of coagulation. Others employ nanotechnology with thermostats that give feedback on tissue properties to ensure better vessel sealing.

The ultrasonic cutting and coagulating surgical device converts ultrasonic energy into mechanical energy at the functional end of the instrument. A piezoelectric crystal in the handpiece generates vibration at the tip of the active blade at 55,500 times per second over a variable excursion of 50–100 μm. This results in rupture of hydrogen bonds and produces heat, which leads to denaturation of proteins and, eventually, separation of tissue. These effects are reached at tissue temperatures of 60°C–80°C, resulting in coagulum formation without the desiccation and charring caused by the temperatures of 80°C and higher associated with the traditional electrosurgical methods.

Light amplification by stimulated emission of radiation (laser) is a commonly used alternative to electrosurgery, and offers a precise application of energy without the inherent risks of lateral tissue damage and stray current associated with standard electrosurgery. Laser energy is generated when electrons jump from higher to lower energy levels during their circuits around the nucleus. The energy created induces molecular vibration and thermal energy upon contact with the target tissue. The most commonly requested laser, the "argon laser," in laparoscopy is not a true laser. It is an argon beam coagulator, which is a device consisting of an electrode recessed inside a probe through which argon gas is passed. The monopolar energy from the electrode is carried by the jet of argon, which is directed at bleeding tissue to cause hemostasis.

Care should be taken when dividing tissue or establishing hemostasis with high-energy devices, as injury to adjacent structures is possible. A 3–5 mm right-angled hook monopolar cautery is a useful device for dividing tissue and preventing hemorrhage. It is important to make contact with the tissue prior to activation of the monopolar electrocautery in order to avoid arcing of current, which may cause a delayed thermal injury to internal structures. Another form of electrocautery that is available is the 3 mm bipolar cautery forceps, which allows for greater control of the current than with standard monopolar cautery.

Suturing

Intracorporeal suturing requires two needle holders or a needle holder and a grasping device. Any length of suture, with its curved needle, may be directly passed through 5 mm trocars, but not through 3.5 mm trocars unless the curved needle is first straightened. The suture may also be passed through the abdominal wall to avoid the need for a 5 mm trocar if ≤3 mm trocars are utilized.

Laparoscopic extracorporeal-assisted tying is possible, but requires a large cannula at one of the port sites. There are a variety of automatic suturing devices; however, it is important for the endoscopic surgeon to become proficient with nonassisted intracorporeal suturing. Furthermore, the majority of devices have a limited choice of suture material size, and most are not acceptable for complex delicate reconstruction.

Tissue Extraction

The benign nature of most pediatric renal diseases allows specimen removal with little concern for spillage. In transperitoneal laparoscopic approaches, most structures can be extracted from the umbilical trocar site, whereas in retroperitoneal approaches, the site for the specimen extraction depends on its size. This includes segments of bowel, cysts, adrenal gland, biopsies, and nearly anything else compressible. In an infant, these tissues are brought directly through the trocar wound since there are few bags small enough to be of much use. In older children, if a 10 mm trocar is utilized, then endoscopic retrieval bags

may be utilized. Larger structures, such as intact solid kidneys or heminephroureterectomy specimens, may require enlarging a trocar incision to facilitate removal. The umbilical trocar site is typically utilized, or a small Pfannenstiel incision can be performed if it is convenient and remains inconspicuous.

Closure

The same technique is used for all laparoscopic procedures. For wounds of <3 mm, application of a tissue adhesive or adhesive paper strips is sufficient. Closing the fascia for all wounds of >3 mm in diameter is recommended. Fascial closure devices facilitate closure, especially in the obese patient.

POSSIBLE PITFALLS AND SOLUTIONS

Malfunction of the Equipment

Well-trained nurses capable of quickly recognizing and correcting equipment malfunction are mandatory. Since the success of the laparoscopic procedures depends heavily on the proper functioning of the equipment, these cases are best performed when skilled staff are available.

Fogging of the Lens

Initially warming the laparoscope in warm saline or povidone-iodine solution or using commercial defogging fluid may help clear the lens and improve the image. Inadequate vision, on the other hand, may result from a gas leak around the primary trocar. This usually leads to complete collapse of the retroperitoneal space, and an extra purse-string suture around the trocar may help to decrease the leak. Another possible reason for inadequate vision during retroperitoneoscopy is a peritoneal tear causing intraperitoneal insufflation. It is then necessary to either convert to a transperitoneal laparoscopic approach or attempt venting the peritoneum using the technique described below. Whether a patient has undergone retroperitoneal surgery before or not, dissection of a previously inflamed retroperitoneum may be suboptimal and frustrating and also dangerous; hence, conversion to open surgery may be considered at any time and should not be considered a failure. Families must be aware of this possibility.

Bleeding

Bleeding may occur while bluntly dissecting, especially the retroperitoneal space; in this case, posterior secondary trocars should be placed and the small vessels must be handled carefully using electrosurgical scissors or the bipolar cautery forceps to secure hemostasis.

Subcutaneous Emphysema

Subcutaneous emphysema may occur due to leakage of CO_2 into the skin around the area of the ports, as the area is larger than the size of the trocar. Signs of this problem include readily palpable crepitus over the flank and abdomen. Treatment for this complication includes either placement of a purse-string suture around the leaking port, changing the trocar to a larger size, or reduction of the insufflation pressure.

Intraperitoneal CO_2 Insufflation during Retroperitoneal Laparoscopic Surgery

If this insufflation occurs prior to the insertion of the two 5 mm accessory trocars, consider transperitoneal or open conversion.

If this insufflation occurs while inserting the secondary trocars (mainly the medial one, superior to the iliac spine), then consider insertion of a Veress needle or an angiocath at the level of the umbilicus intraperitoneally to deflate the peritoneum and change the site of secondary trocar insertion. Since there is intraperitoneal CO_2 insufflation, the risk of injury to the bowels with the Veress needle or angiocath is minimal.

POTENTIAL COMPLICATIONS

Laparoscopic surgery always carries the risk of inadvertent injuries, more common during the learning curve, and increasing experience may lead to a decrease in the complication rates. Since most of the injuries occur during blind access maneuvers with a Veress needle or trocars, the open technique is recommended. Generally, complications that may occur in laparoscopic urological procedures are dependent on the organ operated on.

Great vessel injury may occur from laparoscopic access or dissection. *In children, the distance between the abdominal wall and the great vessels may be as little as 5 cm.* To avoid vascular injury secondary to access, it is advisable to tailor the length of the trocars to the patient age and body habitus. The hallmark features of vascular injuries include either bloody return from the injury site or rapid deterioration of the hemodynamic status of the patient. Once extensive vascular injury is suspected, the trocar should be left in place and an open exploration should be performed. If minor vascular injury is encountered during dissection, such as laceration to the gonadal vessels or adrenal vessels, hemostasis can potentially be achieved laparoscopically through the use of the clips, staples, or ligation.

Bowel injury is a risk of both transperitoneal and retroperitoneal laparoscopy. Because the bowel is out of sight during retroperitoneal procedures, injuries may occur during trocar insertion or dissection secondary to lacerations or thermal injuries from electrocautery. If bowel injury is identified during laparoscopy, it is best dealt with at the time of occurrence. If the surgeon is laparoscopically skilled, the bowel may be repaired using a laparoscopic approach; otherwise, a general surgery consult is recommended. Delayed presentation of bowel injury may occur, and in order to differentiate ileus from bowel injury, a high clinical suspicion should be present. For instance, localized pain at the trocar site associated with fever and leucopenia may be a manifestation of bowel injury.

Furthermore, patients with high suspicion of bowel injury should undergo imaging to rule out gas under the diaphragm, although this can be confusing early on, as CO_2 might persist from insufflation.

We believe that a contaminating injury to the small or large bowel is best handled by open repair with or without proximal fecal diversion. In addition, injuries to the liver or spleen may occur while performing laparoscopic retroperitoneal surgery. If the injuries are superficial, attempts to control the injury laparascopically with gel foam or with an argon beam coagulator may be undertaken; also, open exploration is recommended. Since these injuries may go unnoticed, inspecting the peritoneal or retroperitoneal space upon access and prior to exiting is of paramount importance.

Finally, port-site herniation may occur in 3 and 5 mm trocar sites. Most of the time, it is the omentum that herniates through the port site. This usually requires taking the patient to the operating room for definitive management. A few published reports state that 3 and 5 mm trocar sites should be closed; however, no definitive algorithm exists. It is at the discretion of the surgeon whether closure of these wounds is warranted. Nonetheless, since trocar site closure in the pediatric patient is relatively straightforward, one should consider it in order to prevent the potential complication of herniation. Our approach has been at all times to attempt to close trocars that are larger than 3 mm.

MULTIMEDIA FILES AVAILABLE ONLINE (www.crcpress.com/cw/Docimo)

VIDEO 11.1A Describes abrupt changes in physiological parameters prior to CO_2 insufflation.

VIDEO 11.1B Describes abrupt changes in physiological parameters after CO_2 insufflation.

VIDEO 11.2 Simple access through the umbilical ligament and fascial purse-string suture application.

VIDEO 11.3A Depicts access for two single-port devices that are available commercially: GelPOINT from Applied Medical.

VIDEO 11.3B Depicts access for two single-port devices that are available commercially: SILS port from Covidien.

VIDEO 11.4A Animation depicting the different anatomical details and trocar positions.

VIDEO 11.4B Retroperitoneal access–note the anteriority of Gerota's fascia and posteriority of the psoas muscle.

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CHAPTER 12

Pediatric Fluid Management

William Waldrop and Jake Christensen

INTRODUCTION

Appropriate and well-designed fluid management strategies have been shown to significantly impact patient outcomes from surgical intervention. Indeed, the science of evidence-based fluid administration has advanced considerably in the last 50 years since the publication of the seminal paper by Holliday and Segar.[1] Protocol-based fluid therapy has been shown to impact the incidence of cardiopulmonary events,[2] duration of hospitalization,[3] wound healing, and bowel motility,[2] in addition to its known effect on postoperative nausea and vomiting.[4]

The notion of manipulating fluids to treat patients was first advocated during the cholera epidemic in Britain during the 1830s.[5] A 22-year-old medical graduate, William O'Shaughnessy, described the common practice of bloodletting with emetics as potentially harmful, and reported in the *Lancet* the loss of "neutral saline ingredients" upon chemical analysis of the blood.[6] Shortly thereafter, Thomas Latta published the first successful intravenous resuscitation of a moribund woman with cholera in a graphically descriptive case report.[7] The patient went from pallid and near comatose to awake and fully conversant within 30 minutes after aggressive treatment of hypovolemic shock. Despite these early successes, parenteral saline therapy was not widely used for another half century.[5]

The goal of perioperative fluid management is to maintain the intrinsic homeostasis of the human body. This homeostasis is constantly threatened by the surgical experience, whether by acute blood loss, hypothermia, or the body's response to stress. An elegant plan combines the goals of the individual patient's condition with the expected intensity of the surgery.

Fluid management of pediatric patients is further complicated by several factors. These include age-related differences in metabolism, organ maturity, and body compartment volumes. The incidence of iatrogenic hyponatremia, for instance, is unquestionably higher in the neonatal population, given these differences, and can lead to significant morbidity, including cerebral edema and death in healthy patients.[8]

This chapter provides a brief overview of normal fluid and electrolyte homeostasis throughout the perioperative period, with special attention to the differences between neonates and older children. Various options for volume replacement are described, including special situations requiring elucidation, such as blood component therapy and emergent resuscitation. The aim of this chapter is to provide the basic framework for perioperative fluid management of the pediatric patient.

FLUID AND ELECTROLYTE MANAGEMENT

Developmental Considerations

The greatest challenges in determining the appropriate replacement fluid in pediatric patients occur during the first year of life. Because of several age-related changes, including higher metabolic rate, organ maturity, and subsequent fluid compartment volumes, the first year of life does not lend itself to the generation of simple formulas, unlike in older children and adults.

Considering the immense energy requirements of the developing brain and the brain's large size relative to the infant's body, the basal metabolic rate of preterm and term infants is much greater than that of a child per kilogram of body weight. The basal metabolic rate is the amount of energy per unit time required to power the human body at rest. In preterm infants, this rate has been calculated at 58 kcal/kg/24 hours; the respective values for term and 2-week-old infants are 32 and 48 kcal/kg/day.[9] This rate is roughly increased three- to fourfold over the child and adult value of 15–20 kcal/kg/day. The basal metabolic rate also does not include the energy requirements for growth, which persist throughout puberty and are highest in the first year of life.

Similarly, the infant is challenged because of organ immaturity. The gastrointestinal tract has a diminished capacity for nutrient absorption, as evidenced by the rapid transit time for formula and breast milk. Likewise, the immaturity of the liver cannot support the formation of glucose in the fasting state (gluconeogenesis), which has direct effects in the perioperative period. Most notably, the immature kidneys have both diminished activity (renal blood flow and glomerular filtration rate) and the inability to concentrate urine effectively (due to suboptimal osmolar gradients). Functionally, this results in greater water loss, although this problem is somewhat ameliorated by increased antidiuretic hormone (ADH) secretion with major surgery. The issue of urine concentration becomes less acute by 3 months of age, given the rapid development of sodium concentration gradients.

Electrolyte Requirements

Sodium and potassium are the major osmotically active cations in the body, with sodium predominating the extracellular space, and potassium the intracellular fluid compartment. Counteracting the electrical charge, chloride and bicarbonate are the major anions within the extracellular space. The homeostasis of electrolytes at the cellular level is tightly regulated by active cellular pumps and passive diffusion of free water, which maintains the concentration gradient essential for cellular function.

Physiologic losses of sodium, potassium, and chloride occur by renal excretion. Bicarbonate is the primary acid–base buffer in the extracellular fluid. Pathologic conditions that might interrupt homeostasis for sodium and chloride include active losses in the gastrointestinal tract (diarrhea or vomiting), pleural effusions, or ascites.[10] As "water follows salt," the primary electrolytes of concern for fluid management are sodium and chloride, which determines the major component of osmotically active material in the extracellular fluid, and hence the intravascular volume. Likewise, the total body potassium concentration is critical to normal cellular functions, most notably the electrical activity of the heart and muscle contraction.

The daily maintenance requirements for sodium chloride and potassium are 3 and 2 meQ/100 cal/day, respectively, in children.[11] These requirements were first described in the paper by Holliday and Segar in 1957,[1] and have stood the test of time remarkably well. The commonly used maintenance fluid D5 1/2 normal saline plus 20 meQ/L potassium chloride is based on these daily electrolyte goals.

Free Water Requirements

The utilization of water by the body directly reflects the metabolic rate. As described above, preterm and term infants therefore have a much greater requirement at baseline for free water. In addition, pathologic states that might increase the metabolic rate (e.g., hyperthermia, infection, and cardiac exercise) will dramatically increase the amount of excess free water required to maintain the intravascular space, the ultimate goal in perioperative care. Water can also be "lost" by increased sweat (fever), stool (diarrhea or vomiting), or insensible losses (evaporative loss from an open abdomen). Functional loss of water by sequestration in the cellular interstitium, commonly known as "third spacing," occurs during inflammatory insults, such as surgery or sepsis, and renders the fluid incapable of organ function, such as oxygen delivery by cardiac output or waste removal by the kidneys.[11] Fortunately, if monitored appropriately, most of these variables are within the control of the team caring for the patient.

The production of 1 cal of energy requires net consumption of 1 mL of water by definition. The requirement for free water is therefore a direct expression of the metabolic rate. The basis for daily caloric requirements was elucidated by Holliday and Segar in 1957,[1] and remains the foundation for hourly maintenance calculations. In this landmark study, the investigators plotted caloric requirements in healthy, hospitalized patients at rest, and discovered three linear relationships based on weight. The first 10 kg of infants and children required the highest supplementation, 100 cal/kg/day. Older patients required an additional 50 cal/kg/day between the weights of 10 and 20 kg, and an additional 20 cal/kg/day for each kilogram from 21 to 70 kg. Divide these numbers by 24 hours in a day, and one arrives at the simple formula for hourly maintenance fluid requirements (4 mL/kg/hour for the first 10 kg, 2 mL/kg/hour for the next 10 kg, and 1 mL/kg/hour for above 21 kg—the 4/2/1 rule; Table 12.1).

TABLE 12.1 Hourly (4/2/1 rule) and daily maintenance fluids according to child's weight

Weight	Hourly fluid requirements	Daily fluid requirements
<10 kg	4 mL/kg	100 mL/kg
10–20 kg	40 mL + 2 mL/kg Above 10 kg	1000 mL + 50 mL/kg Above 10 kg
>20 kg	60 mL + 1 mL/kg Above 20 kg	1500 mL + 25 mL/kg Above 20 kg

Interestingly, Lindahl in 1988 used indirect calorimetry to determine the basal metabolic rate in children under general volatile anesthesia.[12] Given the known effects of metabolic suppression of the brain, liver, heart, and kidney during general anesthesia, it was perhaps unsurprising that energy expenditure was 50% lower than the basal rate calculated by Holliday and Segar.

There are currently no effectively reliable monitors that can describe a patient's intravascular volume status. Despite many attempts to link central venous pressure, pulmonary capillary wedge pressure, and transesophageal Doppler to intravascular status,[13] none of the technologies has proved statistically superior. Instead, the mainstay of intravascular assessment remains clinical. In the appropriate clinical milieu, vital sign analysis and fluid responsiveness (the patient's response to fluid bolus) are the clinical determinants of normal intravascular status. Also, the urine output can be assessed on an hourly basis to ensure adequate preload for end-organ function (>0.5 mL/kg/hour should be targeted during surgery).

Glucose Management

There are many known risks for both hypo- and hyperglycemia during an operation. The risks of both are compounded during general anesthesia, as neither can be diagnosed without clinical suspicion in the anesthetized patient. Hypoglycemia carries the known risk of seizures and brain damage, especially in the vulnerable neonatal population.[11] Evidence suggests a very low incidence of hypoglycemia in the perioperative period (<1%) despite prolonged fasting and the majority of patients not receiving intraoperative dextrose.[14] The exception to this rule appears to be neonates, whose minimal liver glycogen stores place this patient at exceptional risk for hypoglycemia. A 1% dextrose solution with lactated Ringer's is emerging in the literature as an appropriate solution to provide neonates with a glucose floor, targeting euglycemia with a glucose level of 65–120 mg/dL.[15] Glucose given

at 120–300 mg/kg/hour maintains an acceptable blood glucose level and prevents lipid mobilization in infants and children.[11]

Intraoperative infusions of dextrose-free isotonic solution should be routine for older children for most procedures. The stress response from surgery will lead to an increase in blood glucose levels in most patients, which tends to correct within 2–3 hours of surgical incision. Persistent hyperglycemia can induce an osmotic diuresis, placing the patient at risk for dehydration and electrolyte disturbances if not closely monitored. Animal studies also favor hypoxic-ischemic brain and spinal cord injury with prolonged hyperglycemia.[16] Frequent laboratory monitoring of glucose level is the only way to avoid these complications.

FLUID COMPARTMENTS

Total Body Water

The human body is composed mostly of water, ranging from 80% of body weight in the preterm infant to around 60%–65% by a child's first birthday. The water fraction of body weight remains remarkably consistent through adulthood at around 60%. Total body water (TBW) can be thought of conceptually as divided between intracellular fluid and extracellular fluid (Figure 12.1). The infant has an excess of extracellular fluid relative to an older child, supporting a larger fraction of intravascular volume. As the child grows, the intracellular component becomes more prominent, as cellular mass expands, including fat cells and muscle.

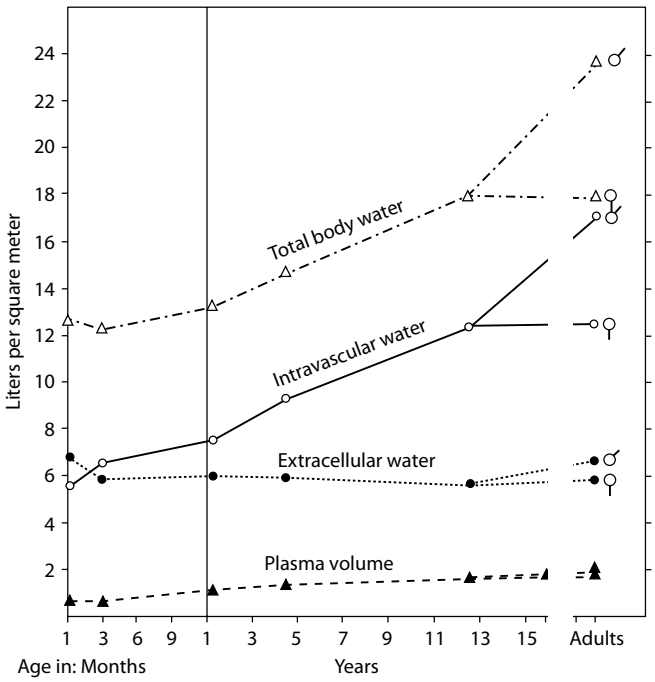

FIGURE 12.1 Changes in TBW, extracellular water, intracellular water, and plasma volume in liters per square meter in infants and children and the corresponding values in adults.

Extracellular Fluid

Extracellular fluid can be further subdivided into transcellular fluid, interstitial fluid, and intravascular volume. The transcellular fluids constitute a minor portion of the extracellular compartment, around 1%–3% of body weight. This includes cerebrospinal fluid, pleural and peritoneal fluids, gastrointestinal secretions, synovial fluid, and the aqueous and vitreous humors of the eyes.[17]

The interstitial component is high in term babies, at around 45% of TBW. By adolescence, this drops to around 20%. The importance of the interstitium in fluid management cannot be overstated. Because the interstitium rapidly equilibrates electrolytes and water with the intravascular space, the interstitium becomes an important reservoir for fluids given to the patient. During surgical stress and sepsis, the interstitium becomes the "third space," expanding in potential volume to be mobilized after the stress has abated several days later.

Intravascular Volume

The most critical space to understand in children is the intravascular volume. Because of an infant's high ratio of body surface area to weight and increased metabolic rate, the intravascular volume is increased for compensation. The normal term newborn has a blood volume of 90 mL/kg. As the child grows and becomes more proportional to weight, the blood volume decreases to 80 mL/kg by 10 years of age. Adolescents and adults have an average circulating blood volume of 65 mL/kg.[18] These calculations have important implications for dosing blood products, as discussed below.

FLUID REPLACEMENT SOLUTIONS

Crystalloid Solutions

There is an increasingly complicated list of fluids to choose from to administer to patients. Understanding the basic composition of these fluids will help the physician decide which of them should be administered. Crystalloids are classified according to how closely they approximate the osmolarity of the extracellular compartment: hypotonic, isotonic, and hypertonic. The pediatric population has a mean serum osmolarity of 284.2 ± 6.9 mOsm/dL.[19] Crystalloid fluids have the basic composition of electrolyte salts dissolved in sterile water. By varying the electrolyte composition, the tonicity of the fluid changes as well (Table 12.2). Tonicity refers to the portion of total osmolarity that has the potential to induce transmembrane water movement.[20]

Hypotonic

The osmolarity of a hypotonic solution is less than that of the extracellular fluid compartment. More than half a century ago, Holliday and Segar[1] calculated daily free water requirements, energy expenditure, and daily electrolyte requirements. Historically, the use of hypotonic maintenance fluids attempted to replace normal hourly expenditures and is not meant as a volume expander or for deficit replacement. Using these fluids as volume expansion places

TABLE 12.2 Crystalloid solutions

Solution	mmol/L						
	Na	Cl	K	Dextrose	Ca	Lactate	Osmol
D5W				50 g/L			252
D3.3/0.3% sodium chloride	51	51		33 g/L			269
D5/0.2% sodium chloride	34	34		50 g/L			321
D5/0.45% sodium chloride	77	77		50 g/L			406
0.9% sodium chloride (normal saline)	154	154					308
Lactated Ringer's	130	109	4		104	28	272
Lactated Ringer's with 5% dextrose	130	109	4	50 g/L	104	28	524
3% sodium chloride	513	513					1027

the patient at significant risk of hyponatremia, as well as dilution of other electrolytes. An ongoing controversy exists regarding the best composition for maintenance fluids. When determining the proper solution to administer, careful thought as to the patient's requirement of water, salt, and glucose should be undertaken. A 5% dextrose in water solution is hypotonic, but has an osmolarity that approximates plasma. This osmolarity therefore prevents the hemolysis that would occur with an infusion of pure water.[21]

Isotonic

Isotonic fluids, such as normal saline and lactated Ringer's, approximate the osmolarity of the extracellular compartment. Normal saline is a saltwater solution and is composed by dissolving 9 g of sodium chloride into 1 L of sterile water to produce 0.9% sodium chloride solution. These fluids are widely used for expansion of the extracellular compartment, deficit replacement, or rehydration. As isotonic fluids do not change the extracellular/intracellular osmotic gradient, no net fluid shift occurs. Isotonic crystalloid fluid added to the vascular compartment is quickly redistributed between the intravascular and interstitial compartment. This can lead to significant tissue edema.

Hypertonic

Hypertonic fluids, for example, 3% sodium chloride, are hyperosmolar relative to plasma. In addition to expanding the intravascular compartment, they will expand the extracellular volume and increase its osmolarity, thereby changing the extracellular/intracellular osmotic gradient. For this reason, a free water shift from the intracellular to the extracellular compartment will occur. The indications for this fluid are limited, and the volume administered should be relatively small. The most well-known indication is for traumatic brain injury, as 3% sodium chloride can reduce brain edema and lower intracranial pressure. Hypertonic saline has also been studied in situations of massive hemorrhage, given the desire to stabilize intravascular volume but minimize further bleeding with higher blood pressures.[22]

Colloid Solutions

Colloid solutions are composed of large relatively impermeable molecules that exert intravascular osmotic pressure in order to expand the intravascular space. Colloid solutions are designed to remain intravascular and not to equilibrate to the interstitial compartment. However, in pathologic states, such as surgery, capillary leakage of these fluids does occur.[23] For these reasons, colloids should not be used as maintenance fluid for insensible losses but for volume expansion to replace acute blood loss. Examples of colloid solutions are the following: starches, albumin, and gelatins.

Starches

Naturally occurring starches are rapidly metabolized by amylase in the plasma. Hydroxyethyl starch (HES) is a synthetic colloid modified from naturally occurring starches and is highly resistant to metabolism. HESs are available in differing concentrations (3%, 6%, and 10%) and differing molecular weights (low, <70 kDa; medium; and high, >450 kDa). The C2:C6 hydroxyethylation substitution results in prolonged duration of action without increasing the known side effects. For this reason, the newer generation of HES has a high C2:C6 ratio but low molecular weight.[24] Side effects of HES include its anticoagulant effect (with volumes greater than 1.5 L in adults), potential to worsen renal function, and pruritis resistant to therapies in up to 22% of patients.[24]

Albumin

Albumin is derived from pooled human plasma and is osmotically equivalent. It remains the standard colloid administered in infants and neonates. Albumin has a molecular weight of 69 kDa. Allergic reactions are possible but significantly reduced in comparison with the other colloid solutions.[25] Albumin has been shown to have higher mortality than saline when administered as acute resuscitation to critically ill traumatic brain injury patients.[26]

Gelatins

Gelatins are polypeptides produced by degradation of bovine collagen. While use in Europe is common, no gelatins are currently available in the United States due to the highly allergic propensity of initial preparations.[24] Gelatins are a less effective colloid, having the relatively

small molecular weight of approximately 35 kDa. The benefits of using gelatins for volume expansion include rapid degradation with renal clearance, allowing proponents to maximize volume expansion within the intraoperative period.[24] Their efficacy in infants is in doubt; a Cochrane review of preterm infants found gelatins to be equal to no fluid therapy when assessed for necrotizing enterocolitis.[27]

PERIOPERATIVE FLUID MANAGEMENT

Preoperative Fasting

Fasting guidelines are for the purpose of reducing the risk of regurgitation in the unconscious state and subsequent pulmonary aspiration. Excessive fasting times can have deleterious effects, such as decreased intravascular volume, hypoglycemia, hunger, irritability, and dissatisfied parents. Current well-established guidelines allow clear liquids up to 2 hours prior to anesthesia in the otherwise healthy pediatric patient.[28] Other guidelines are as follows:

- 2 hours after clear liquids
- 4 hours after breast milk
- 6 hours after infant formula or nonhuman milk
- 6 hours after a light meal
- ≥8 hours after a full meal

In the healthy infant or child, these guidelines will have minimal physiologic or metabolic effects. Decreased fasting times will improve intravascular volume, leading to a more stable induction of anesthesia and ease in obtaining vascular access. Chewing gum has been shown to significantly increase gastric volumes above controls.[29] If gum has not been swallowed, providers treat this as a clear liquid and impose a 2-hour restriction. In children who have undergone trauma, gastric transit times are reduced and unpredictable, and there is no safe fasting time.[28]

Preoperative Fluid Therapy

Healthy outpatients who have followed the fasting guidelines outlined do not require preoperative fluid administration. Venous access can be delayed until induction of anesthesia in many of these healthy young patients. However, there are still patients who will not fit these criteria. Dehydration can arise from many clinical scenarios, such as prolonged fasting, vomiting, diarrhea, sepsis, burn patients, and diabetes. The accurate assessment of fluid status will guide fluid management throughout the perioperative course. Presenting history that supports dehydration includes recent vomiting or diarrhea, decreased urine output (i.e., number of wet diapers), decreased oral intake, decreased activity level, and acute weight loss. During physical examination, the providers can assess for skin turgor and capillary refill time, abnormal respiratory pattern, dry mucous membranes, sunken fontanelle, sunken eyes, weak pulse, increased heart rate, cool extremities, and overall appearance. Laboratory data supporting dehydration include an elevated bun/creatinine ratio, the presence of acidosis with a low bicarbonate value, and an anion gap. In a review of the literature, Steiner et al. found capillary refill time, skin turgor, and abnormal respiratory pattern among the best signs to predict dehydration on examination.[30] Making the accurate diagnosis of dehydration and estimating its severity will require taking all available clinical information into consideration.

Restoring intravascular volume is essential in the preoperative patient. Isotonic fluids, such as normal saline or lactated Ringer's, should initially be used when replacing acute fluid deficits. Maintenance fluids are handled differently. In children, daily sodium and potassium requirements are 2–4 mmol/kg each, which when combined with daily fluid requirements results in a hypotonic solution.[11] Historically, fluid administered as maintenance by pediatricians is D5 1/4 normal saline with 20 mEq/L KCl.[31] The hourly maintenance fluid requirement, the Holliday–Segar method, is described above and based on caloric expenditure calculated from weight.

Infants and young children have reduced glycogen stores. For those at risk of hypoglycemia, a dextrose-containing IV fluid should be administered during the fasting period and extended throughout the operative course until baseline feeds can be reestablished. For those patients who are fasting for prolonged periods of time, total parenteral nutrition (TPN) should be considered. When stopping TPN perioperatively, a dextrose-containing fluid with a similar glucose infusion rate should be started to avoid hypoglycemia.

Intraoperative Fluid Management

Intraoperative fluid losses are primarily isotonic, and therefore are replaced differently from the hypotonic fluids typically used preoperatively for maintenance. Fluid replacement intraoperatively takes into account the maintenance requirements from the fasting period, surgical blood loss, third-space fluid loss, and insensible fluid losses, including that from the surgical field by evaporation. In addition, the surgical stress response promotes an increased secretion of ADH. This increased ADH response results in water resorption in the distal renal tubules and collecting ducts.[32] This free water retention from the increased ADH response, combined with the potentially large isotonic surgical losses, places the patient at risk of hyponatremia if the replacement fluid used is hypotonic with respect to blood.

Published rates of third-space fluid loss vary among operations performed. These losses can be as low as 1 mL/kg/hour for very minor surgical procedures to as much as 15–20 mL/kg/hour for major abdominal procedures, or even as much as 50 mL/kg/hour for necrotizing enterocolitis in premature infants.[11] Younger patients have a larger extracellular fluid volume (45% body weight for neonates vs. 20% for adults), which creates more opportunity for equilibration and third-space loss. Isotonic crystalloid fluids equilibrate across the extracellular fluid compartment. Normal saline is actually slightly hypertonic with an osmolarity of 308 mOsm/L; it is comprised of a sodium concentration of 154 mEq/L and a chloride concentration of 154 mEq/L. When using normal saline for volume expansion in large amounts, a hyperchloremic metabolic acidosis can result. This is due to the normal

saline providing excessive chloride, causing a shift in the strong ion difference (which is one of the main contributors to the standard base excess).[33] Lactated Ringer's actually causes a slight base excess, as it contains lactate that is metabolized to bicarbonate in patients with normal liver function. Lactated Ringer's solution is actually slightly hypotonic with an osmolarity of 273 mOsm/L and has a sodium concentration of 130 mEq/L. When using lactated Ringer's for volume expansion, the perioperative risks of hyponatremia should also be considered.[34]

When acutely volume resuscitating with isotonic crystalloid solutions, an initial bolus of 10–20 mL/kg is usually given, and then cardiovascular stability is reassessed. After reaching 30–50 mL/kg of crystalloid solution, the use of colloid solution (albumin or synthetic colloid) to maintain intravascular osmotic pressure is indicated.[11] Hetastarch is more controversial than albumin, and among pediatric anesthesiologists, it is avoided in the premature and newborn infant.[11] Hetastarch at large volumes has an anticoagulant effect; at volumes greater than 20 mL/kg, it has been demonstrated to increase the prothrombin time.[35] Blood loss is replaced in a three-to-one volume with crystalloid solutions due to its equilibration across the extracellular compartment, while colloids and blood products are replaced in a one-to-one fashion with blood loss.

Blood Component Therapy

Volume resuscitation with isotonic and colloid solution in the bleeding patient is performed until the decision to transfuse is reached. This decision should be collaboratively discussed between the surgeon and anesthesiologist, as there is no empirical evidence to support a transfusion trigger. Indeed, the decision to transfuse needs to be made based on overall assessment, and should include consideration of the hemodynamic status, extent of ongoing blood loss, disease severity, comorbidities, and lactate and mixed venous oxygen saturation, if available, among other considerations.

In order to make this determination, and the amount of blood products to transfuse, it is necessary to calculate the estimated blood volume (EBV). The EBV is calculated based on the age and weight of the child (Table 12.2).[32] Knowing the allowable blood loss (ABL) will help in making the determination to begin blood component therapy. ABL is calculated as follows (Table 12.3):

$$\text{ABL} = \frac{(\text{Starting hematocrit} - \text{Lowest allowed hematocrit})}{\text{Starting hematocrit} \times \text{EBV}}$$

TABLE 12.3 Estimated circulating blood volume versus age or weight

Age	Estimated blood volume (mL/kg)
Premature infant	90–100
Term infant to 3 months	80–90
Children older than 3 months	70
Very obese children	65

Neonates and infants have a higher ratio of oxygen consumption to blood volume than adults, and the neonatal myocardium works at near maximal levels at baseline. For this reason, the newborn heart may not be able to compensate for a decreased oxygen-carrying capacity by increasing cardiac output.[36] Neonates and infants may also have reduced ability to oxygenate blood due to the presence of cardiac or lung disease. The neonate and infant may benefit from maintaining a higher hematocrit (Hct) for these reasons.[37] It is important to know that one unit of packed red blood cells (PRBCs) is approximately 250 mL and has an Hct that approximates 70%. The usual starting dose is 10 mL/kg, which is expected to raise the Hct by 9%. In order to calculate the volume of PRBCs to administer based on the estimated blood loss (EBL) beyond the ABL, the following formula[37] can be used:

$$\text{Volume of PRBCs to transfuse} = \frac{(\text{EBL-ABL}) \times \text{Target Hct}}{\text{Hct in PRBCs (70\%)}}$$

Blood components are typically used rather than whole blood. This can be more cost-effective, as a single donor unit of blood is split into components and made available to multiple patients. Whole blood contains all clotting factors; therefore, when using component therapy during a massive transfusion situation, care must be taken to prevent a dilutional coagulopathy from occurring. Fresh frozen plasma (FFP) contains 250 mL of plasma in a citrate anticoagulant. FFP at 10 mL/kg raises most factors by 10%, and the fibrinogen level will rise 40 mg/dL when 15 mL/kg is given.[38] An apheresis unit of platelets contains 3×10^{11} platelets in 250–300 mL of plasma. A dose of 10 mL/kg can increase the platelet count by 20,000–50,000.[38]

Many complications can arise during blood component therapy. During massive transfusion when multiple PRBCs have been given, clotting factors will become diluted unless administered concurrently. As a general rule, the platelet count will be decreased by 40% after loss of one blood volume, and by three blood volumes lost, it will be decreased by 70%, assuming no replacement.[37] All blood products contain citrate as a storage anticoagulant. FFP has a considerable amount of citrate, and when given rapidly, it can lead to a reduction in ionized calcium and hypotension. In addition, patients with decreased liver function and neonates are at risk of hypocalcemia and citrate intoxication due to decreased metabolism.[36] Normal saline should be used as the carrier when transfusing blood products, as the calcium in lactated Ringer's may lead to microaggregation and calcium deposition. Care must be taken by the transfusionist to prevent ABO incompatibility, which can result in an acute hemolytic reaction.

Blood transfusion therapy can also lead to transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), and transfusion-associated graft versus host disease (TA-GVHD). TA-GVHD has particular importance in pediatrics and occurs when donor lymphocytes proliferate and cause host tissue destruction.[36] This is mostly a concern in the immunocompromised recipient who cannot mount an immunologic response to donor lymphocytes, such as those with

primary immunodeficiency (e.g., severe combined immunodeficiency, Wiskott–Aldrich syndrome, and DiGeorge syndrome), as well as prematurity, acute blood loss, cardiopulmonary bypass, and neonatal stress.[39] TA-GVHD can occur in the immunocompetent patient who receives blood donated from a biological relative. The related donor lymphocytes may not be recognized as foreign due to their similar haplotypes, and the recipient does not mount an immune response; therefore, the donor lymphocytes proliferate and destroy host tissue.[36] Irradiation of donor units effectively inhibits lymphocytes from proliferating and preventing TA-GVHD; therefore, it should be employed whenever TA-GVHD is a risk.[39]

Emergent Volume Resuscitation

During emergent volume resuscitation, the choice of fluid, volume, and rate of administration varies depending on many clinical variables. Early volume resuscitation is initiated with boluses of 10–20 mL/kg titrated to adequate blood pressure, heart rate, quality of peripheral pulses, capillary refill, peripheral temperature, level of consciousness, and urine output.[40] In septic shock, the volume and rate of vascular loading has prognostic significance; in general, the younger the child, the greater the volume of fluid loading to body weight.[11] If patients do not respond to this initial therapy, consideration for invasive monitoring to guide therapy should be given. In the instance of trauma with ongoing blood loss, volume resuscitation should be managed in order to minimize the lethal triad of hypothermia, acidosis, and coagulopathy.[41] Institutional use and availability of massive transfusion protocols significantly reduces the amount and cost of the blood components used.[42] Recent studies of massive transfusion in combat trauma with life-threatening hemorrhage have been associated with decreased mortality with the earlier use of hemostatic blood products. Emerging literature suggests transfusion at a 1:1:1 ratio of PRBCs to FFP to platelets.[43]

Postoperative Fluid Management

In most instances of day surgery, the postoperative pediatric patient will be allowed to take fluids by mouth within the first few hours. When oral intake is not allowed, such as with bowel surgery, then intravenous fluid therapy must resume. Isotonic fluids are recommended in the postoperative period, as hyponatremia is the most common electrolyte disorder. Prepubertal children are more susceptible to perioperative hyponatremia, which can occur after elective surgery and can cause severe hyponatremic encephalopathy, resulting in death or permanent brain damage.[44] Increased ADH secretion during surgery and administration of hypotonic solutions can lead to a state of hyponatremia, which patients remain at risk for in the postoperative period. Signs of cerebral edema include decreased consciousness, disorientation, vomiting, and in severe cases, seizure activity refractory to antiepileptics.[11] By using isotonic solutions in the operative and postoperative period, hyponatremia and its severe consequences can be prevented.

SUMMARY

Fluid therapy in the pediatric patient requires careful consideration of the patient's developmental stage. Changes in metabolism, organ maturity, and fluid compartments pose additional challenges. Crystalloid, colloid, and blood component therapy should be used thoughtfully and with evidence of patient need. Laboratory reevaluation is encouraged to assist in achieving homeostasis and improved patient outcomes.

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CHAPTER 13

Problems with Transitional Care

Dan Wood

CASE 1: CONCERNS WITH PENILE APPEARANCE IN EXSTROPHY

You receive a new referral to your clinic of a 17-year-old boy born with bladder exstrophy. He has had many previous operations, but 5 years ago, in order to achieve continence, his pediatric urology team created a continent urinary diversion and augmented his bladder with an ileocystoplasty. He is dry and happy with no apparent urological issues (you can assume his follow-up for this is dealt with). However, during your consultation he expresses concern about his penile appearance in relation to size and his ability to have penetrative sexual intercourse with a partner. He also tells you that he has had three attacks of epididymitis in the last year.

Questions

1. How would you begin to assess his penile function? What questions would you ask? How could you investigate him?
2. What are the anatomical limitations in reconstructing an exstrophy penis?
3. On further investigation, you discover a marked dorsal chordee. What are your operative options? What major risks would you explain to the patient?
4. What are the concerns relating to the urethra? How would you manage these?
5. Why do you think he has suffered epididymitis? How would you address this?

Discussion

1. It is vital to take a thorough sexual history as a baseline. This needs to include whether he has attempted penetrative intercourse, and if so, was he able to achieve that with a partner? For some, the reconstructive result is excellent and they need reassurance that they can and will go on to have good relationships on both an emotional and a physical level. You need to document whether he currently achieves normal erection, orgasm, and ejaculation. Ejaculation in bladder exstrophy may be limited for two reasons. The first may be that the bladder neck surgery may have caused damage or obstruction to the ejaculatory ducts, resulting in a reduction in ejaculate volume. The second issue is the absence of the propulsive bulbocavernosus muscle that creates the propulsion seen in normal ejaculation. It is also important to ask him about the shape of his penis when erect. One corpora may be more scarred than the other, creating a curvature, or it is common to see a very severe dorsal chordee with the penis parallel to the abdominal wall—making intercourse impossible. Depending on the outcome of your discussion, you may recommend an artificial erection (discussed in the next section) or imaging—an MRI may be helpful if operative intervention is planned.
2. Aside from previous surgical interventions, it is important to understand that the exstrophy penis has corpora that are up to 50% shorter than those of a normal penis. This is important in counseling patients, as the exstrophy penis is typically shorter and wider than normal, and no surgery is going to change that to a "normal" situation. A wide pubic diastasis may compound this impression. The neurovascular bundles are commonly more laterally placed in the infant exstrophy penis, but the position of these may become less predictable with surgical intervention, particularly if the corpora have been rotated. The other limitation may the position and length of the urethral; this is discussed in the later section. These factors are best assessed with an artificial erection under general anesthesia (GA). Even after reconstruction including corpora corporotomy, the blood flows to each corpus are usually separate. The best way of assessing the corpora involves insertion of large-bore butterfly needles into each side and infusion with pressurized saline (Figures 13.1 and 13.2). This allows regular inflation and deflation throughout if

FIGURE 13.1 Artificial erection being performed on a patient with bladder exstrophy and a marked dorsal chordee.

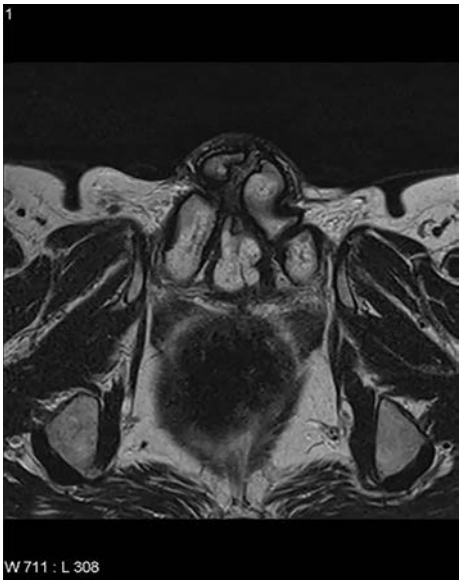

FIGURE 13.2 MRI that demonstrates the distraction of the two corpora with the urethra passing between them.

necessary and avoids the need for a tourniquet, which may mask a very proximal defect or curvature. The patient should be woken after the artificial erection and counseled about the risks and benefits of surgery.

3. The surgical approach with a dorsal chordee may vary depending on the findings of the artificial erection. In principle, the penis will need to be degloved—this is performed after completing an artificial erection to identify the problem. Although a circumferential incision is made, this often needs to be coupled with a longitudinal incision. The location of this is a matter of judgment and may be either ventral or dorsal. This then allows effective degloving of the penis—with dissection of scar tissue. Care needs to be taken in identifying the location of the urethra and the neurovascular bundles. Once the neurovascular bundles have been isolated with a vessel loop, a further artificial erection will identify the precise location of the difficulty and correction can be undertaken. The patient needs to be warned about erectile dysfunction, loss of sensation, skin loss, and penile shortening
4. The urethra in exstrophy is in the epispadic position, and part of the initial reconstruction will have been to try and normalize its position. In assessing a dorsal chordee, it is important to know where the urethral is in relation to the scar tissue between the base of the penis and the anterior abdominal wall. It may be very superficial. If this is the case, then it will be taking a straight-line course to its point of termination. If the penis is straightened, this will increase the distance that the urethra must reach in order to maintain a terminal meatus, as the objective of the operation is to increase the distance between the tip of the penis and the abdominal wall by releasing the chordee. In this situation, the function of the urethra is important. In this young man's case, it is functioning as a seminal conduit. And the creation of a neourethra with buccal mucosa (for example) would almost certainly stenose and fail; therefore, the patient may have to accept a hypospadic meatus as the price of a more functional erection. If the urethra is used for urination, then urethral reconstruction may be achievable to terminalize the meatus.
5. It is reasonably common for these young men with exstrophy and/or epispadias to suffer epididymitis in adolescence. It can be very difficult to treat, as the pathology almost certainly occurs as a result of unavoidable intervention at the bladder neck as part of earlier reconstruction. Conventional antibiotics may be enough to resolve the problem, but if not, testicular damage may result and, in some instances, a vasectomy on the affected side only may be the best way to avoid further testicular damage and preserve fertility.[1–4]

CASE 2: XY DSD

You are asked to see a 16-year-old female patient. You are told that she has a karyotype of 46 XY and has been diagnosed as having complete androgen insensitivity syndrome (CAIS). She has an absent vagina, and you are being asked for help in reconstructing her vagina by your gynecology colleague. She does not have urological symptoms.

Questions

1. What is the current classification of disorders of sex development (DSDs)?
2. What is the classical presentation of a patient with CAIS? What would you expect to see as external and internal genitalia?
3. How would you advise her regarding her gonads? What is the risk of malignancy?
4. What are her options for vaginal reconstruction?

Discussion

This is a complicated subject and worth reading about. There are some excellent texts, and this short summary is not a replacement for them. The elements of sex development are chromosomal, gonadal, and hormonal. Any of these may take an abnormal course in either isolation or combination. Remember that the default for sex development is female, and that a fetus has to have particular factors (chromosomal, gonadal, and hormonal) in place to make it male. In examining a patient, try to think about whether he or she is an overvirilized female or an undervirilized male. Table 13.1 shows the current (2012) accepted nomenclature.

TABLE 13.1 Current classification of DSD

Classification	Examples
46 XX DSD	Congenital adrenal hyperplasia (by far the most common)
46 XY DSD	Androgen insensitivity syndromes, 5-alpha-reductase deficiency, abnormal MIS activity; there are other examples
Gonadal dysgenesis	A failure in gonadal development with a spectrum of presentations
Ovotesticular DSD	Both ovarian and testicular tissue present (previously called true hermaphroditism)

FIGURE 13.3 Gonadectomy being performed on a patient with XY female DSD (CAIS).

1. If the androgen blockade is truly complete, this young patient will be born with a phenotypically female appearance. If there is a partial blockade, there may be some androgenous features, such as clitoromegaly. In complete androgen insensitivity, it would be very possible to raise this baby as a girl with no knowledge of any concerns. Close inspection of the genitalia may reveal the lack of a vagina or a small pit—this may be very difficult to spot. There is usually no evidence of female internal genitalia; these do not develop because of testicular excretion of Müllerian inhibiting substance (MIS). Under these circumstances, this girl is likely to present with primary amenorrhea.
2. The gonads are most commonly intra-abdominal testes—they may be felt in the groin in some. In infancy, the concern relating to gonads is that any sensitivity to androgens (i.e., a partial insensitivity syndrome) would result in androgenization when she reaches puberty, i.e., clitoral growth and male pattern physical development and hair growth. On these grounds, some would argue for early removal (see Figure 13.3). Increasingly, patient groups are suggesting that they have a better puberty and a greater sense of well-being with the background production of testosterone. In fact, some female XY DSD patients are deliberately retaining their gonads. The malignant risk has always been thought of as low, but there are no data under these circumstances and follow-up arrangements for the gonads are very difficult to plan. The other important aspect to this is that retention of the gonads may lead to the ability to harvest spermatozoa and potentially achieve fertility via surrogacy.
3. This girl is unlikely to need any surgery in childhood and may not even be aware of her diagnosis until puberty and amenorrhea trigger investigation. In order to create a functional vagina, she may be able to dilate if there is a pit. In the absence of scar tissue, this would be an excellent option for her. This can be achieved using handheld dilators or the laparoscopic implantation of a Vechietti device (see Figure 13.4). Further reconstructive options exist with the use of perineal skin, peritoneum, or bowel substitution. This is a decision that needs to be made on an individual patient basis, and care should be provided by a multidisciplinary team. The surgery can be complex, but it is very important to account for the shock that disclosure of the diagnosis may create, and it is imperative that the multidisciplinary team includes psychology, gynecology, endocrinology, genetic, and urological support.[4–6]

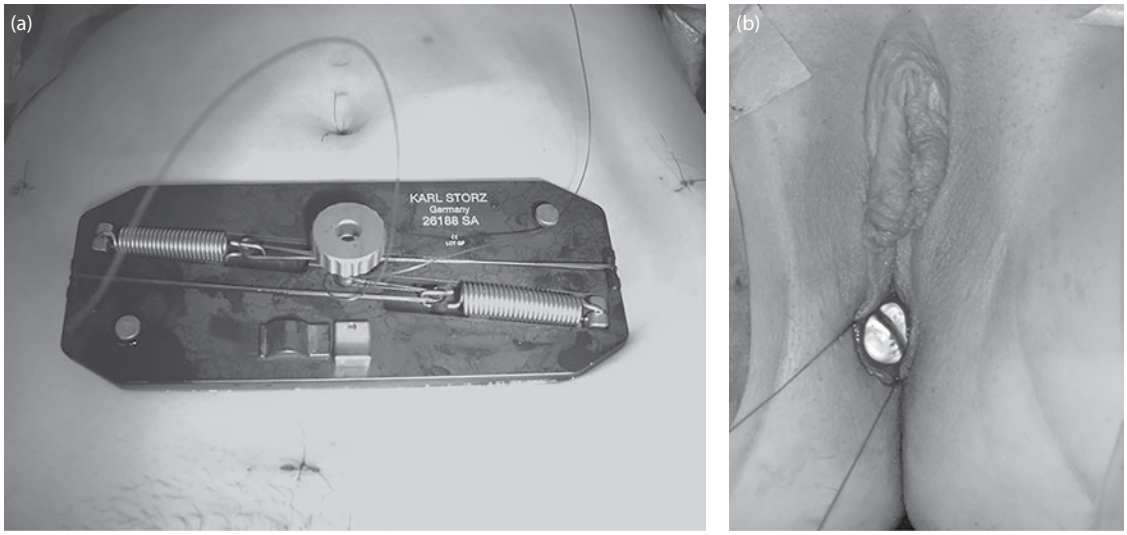

FIGURE 13.4 Device used for a Vechietti vaginoplasty. (a) The device sits on the anterior abdominal wall with tensioning sutures passing laparoscopically to the dilator. (b) The tensioning sutures sit in the vaginal dimple and can be tensioned to create a vaginal tract.

CASE 3: WORSENING RENAL FUNCTION

An 18-year-old gentleman is transferred to your care. He was born with posterior urethral valves. His clinical course has been relatively straightforward through childhood. His last glomerular filtration rate (GFR) was performed 5 years before you see him and was measured as 106 mL/min/1.73 m^2. He is well, but you identify that he has an 800 mL capacity with a 400 mL postvoid residual, and his latest GFR comes back as being 60 mL/min/1.73 m^2.

Questions

1. How would you approach this gentleman's further evaluation?
2. What options do you have regarding his bladder management?
3. Which noninvasive tests should you perform at each clinic visit?
4. Describe how you would obtain pre-operative consent from a patient in order to operate and give the patient a continent catheterisable stoma.

Discussion

1. He needs video urodynamics to understand his bladder function. If there is doubt about upper tract drainage, a MAG3 renogram could be used. Other tests should include evaluation of proteinuria with a protein–creatinine ratio and a serum creatinine. A cystoscopy will rule out a ureteric stricture as a cause of difficulty emptying and ensure visual assessment of the bladder neck.
2. His bladder should be drained completely to avoid urinary tract infections (UTIs) and further renal deterioration. A trial of alpha-blockers may improve emptying if he has a hypertrophic bladder neck. Urethral self-catheterization may be possible, but these boys are normally sensate and therefore find this very uncomfortable. However, it is an important intervention to try, as it does not have any irreversible sequelae. Pediatric series have reported bladder neck incision to improve drainage. The concerns around this relate to induced retrograde ejaculation and the potential impact on fertility (this may already be impaired due to intrinsic semen parameters in valve patients). In considering this, a baseline semen analysis needs to be performed, and if sperm are present, banking should be offered. If the bladder remains a likely culprit and all other avenues fail, a continent catheterizable channel may be the only alternative.
3. It is our practice to perform a urine dipstick to look for proteinuria and to take the blood pressure at each visit. This allows us to highlight concerns earlier and involve nephrological support earlier, when required. Renal preservation with angiotensin-converting enzyme (ACE) inhibitors or receptor antagonists may be used to slow further renal deterioration.
4. The procedure could be performed through either a midline or a Pfannensteil incision. The appendix is used when present and possible (10%–15% are not usable); if not, we make a Monti channel from the small bowel.

FIGURE 13.5 Patient catheterizing his umbilical Mitrofanoff channel.

This is anastomosed to the native bladder to create a flap valve effect. In a good-volume safe bladder, there is no need for an additional cystoplasty. The channel is made using a size 14 Ch catheter, and this is left in place and the channel activated at 6 weeks (practice varies on this time span from 3 to 6 weeks) (see Figure 13.5). Risks include channel failure, leakage, and stenosis (revision between 30% and 50% in the literature, with the highest rate at the skin level). Small bowel obstruction and fistula should be mentioned. The site should be agreed; the umbilicus and right iliac fossa are the two most common. All patients undergoing a new Mitrofanoff procedure will spend about 90 minutes with our specialist nursing team with a video and other counseling to help them understand the procedure. This appears to be time well invested, as those most unhappy with the procedure complain most about a lack of preoperative information or struggling for postoperative support.[7–9]

CASE 4: BLADDER STONES: CYSTOPLASTY MANAGEMENT

You see a 25-year-old male with ambulant spina bifida in your clinic. He had been lost to follow-up for several years. He has returned because he has developed a suprapubic fistula with clear fluid draining out from it. You discover that he has had a cystoplasty and a bladder neck reconstruction in childhood and has recently had an increase in the number of UTIs he suffers with. Computed tomography (CT) of the kidney, ureter, and bladder (KUB) shows 2 large stones in his bladder (see Figure 13.6).

Questions

1. What are the long-term complications of having bowel in the urinary tract?
2. What factors do you know of that increase the risk of stones in a cystoplasty?
3. How would you remove these stones?

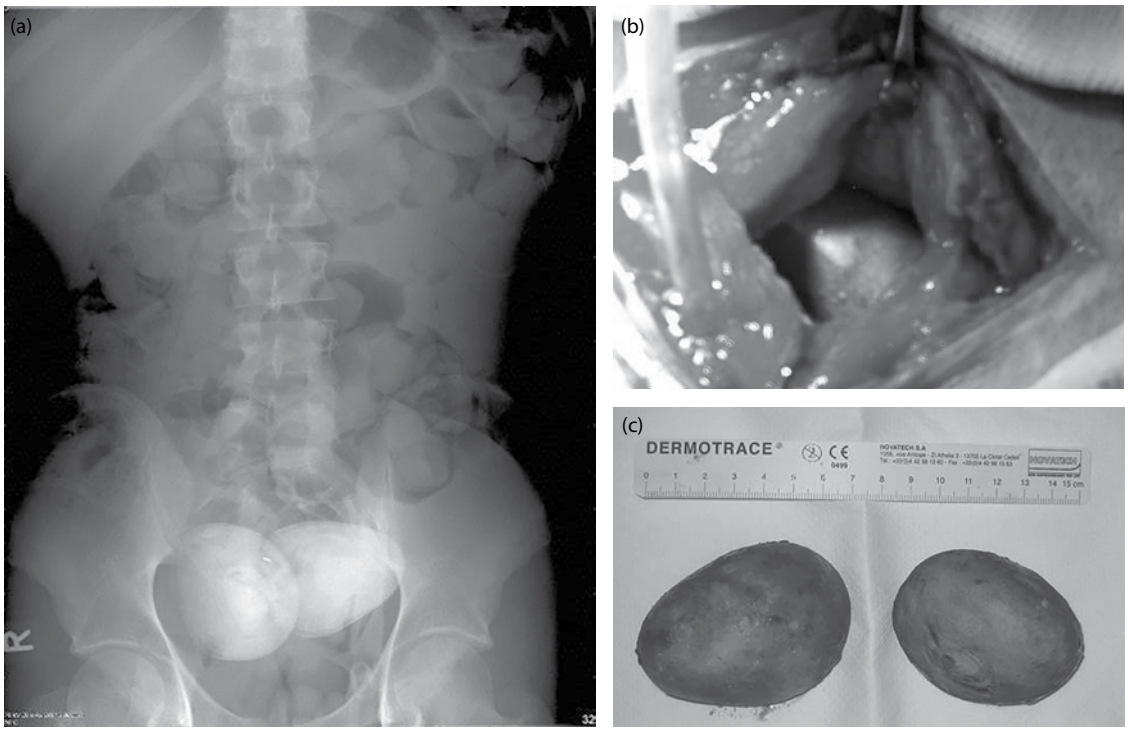

FIGURE 13.6 X-ray (a), open removal (b), and removed bladder stones (c) from a patient with a cystoplasty.

4. What protocol would you use for regular follow-up of patients who have had cystoplasty?
5. What are the arguments for and against routine regular cystoscopy of a patient who has had a cystoplasty?

Discussion

1. The most common complications are mucus production and biochemical changes. When bowel is grafted into the urinary tract, it still continues to behave as a bowel—including its tendency to produce mucus. There has not been any treatment that appears to improve this. Some factors, like infection, diet, or pregnancy, may worsen production. A good fluid intake and bladder washouts are an important part of preventing a buildup. Catheter size is also important. A size 14 Ch catheter is ideal, as it will predictably allow mucus to drain; a size 10 Ch is too small and will not. Many people will manage with a size 12 Ch. Metabolic changes are often subclinical, but a net loss of bicarbonate in exchange for chloride and a tendency to absorb ammonium ions will create hypochloremic metabolic acidosis. If the levels are measured as normal or near normal, treatment is unlikely to be needed, but abnormal levels or symptoms require oral replacement with bicarbonate. Other complications include bowel complications (change in bowel function, small bowel obstruction, and fistulae), UTIs (20%–30%), stones (see Figure 13.6), B12 deficiency (depending on segment used), perforation, and the potential for malignant change.
2. The first and most obvious risk for stone is having had a previous stone, and any patient we encounter that has suffered stones in his or her cystoplasty should be given advice about how to reduce the risk of future occurrences. In a paper that examined the characteristics of those patients who did develop stones, the two most significant findings were the low 24-hour volume in stone formers and lower urinary citrate. An increase in fluid intake ($\geq$2.5 L/day), avoiding salty and high-oxalate food (e.g., rhubarb, spinach, chocolate, and peanut butter), and a healthy balanced diet are important preventative steps. Ensuring regular bladder drainage is vital, and weekly bladder washouts are necessary to ensure there is no mucus buildup. Regular imaging follow-up is also essential in order to detect stones early and remove them before they increase in size.
3. The only option for removing these stones is with an open procedure. The patient has had multiple abdominal procedures and his Mitrofanoff channel is catheterized to allow filling of the bladder. An incision between 5 and 10 cm is made (often using an old scar, size dependent on the size of the stone), the bladder is opened between stay sutures, and the stone is lifted out intact. The bladder is closed in two layers and left on free drainage for 10 days.
4. In our institution, once patients are using their cystoplasty and have passed a trial of void or emptying, they are seen at 6 months with an ultrasound, MAG3 renogram, and blood test (including renal function, bicarbonate, chloride, vitamin B12, and full blood count). The blood test and ultrasound are repeated annually, and a GFR is performed every 5 years. Some would argue that a B12 assay is unnecessary if you know which bowel segment has been taken. We have many patients who have had previous surgery and for whom it is difficult to know which segment has been used. Therefore, since a B12 test is cheap and safe, we

perform this routinely as part of our protocol, as the consequences of missing a deficiency are irreversible neurological deficit.

5. Unfortunately, when cancer has been found in cystoplasties, it has been aggressive in nature, and rarely any have been found with annual screening cystoscopy. They are uniformly discovered during screening intervals on the basis of a symptomatic presentation. Therefore, there is very little argument for annual screening, but a much stronger case for clinical follow-up with aggressive investigation of changed symptoms (e.g., pain, hematuria, or new and recurrent UTI pattern).[6,7,10]

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CHAPTER 14

Embryology of the Genitourinary Tract

Steven E. Lerman, Irene M. McAleer, Alan L. Kaplan, and George W. Kaplan

An understanding of the significant events in the embryology of the genitourinary tract is essential to both the diagnosis of congenital anomalies and the interpretation of pathologic findings that result from disordered embryogenesis. We separate the embryology into several small chapters, each relating to sections of the text organized by system. This short chapter serves as a general introduction to the embryology of the genitourinary tract. Embryologic data are synthesized largely from standard textbooks of embryology,[1–4] but are amplified with newer concepts as they seem clinically pertinent. Particular emphasis is paid to genetic and molecular pathways important in genitourinary tract development. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Strategic Plan for Pediatric Urology highlights the importance of understanding the cellular and molecular basis of genitourinary tract development to advance the diagnosis and treatment of these diseases.[5] The material is arranged chronologically as well as by organ (system) to provide a better understanding of the interrelationships between structures. A developmental "timeline" is presented at the conclusion of this chapter for easy reference (see Figure 14.1 later in this chapter).

The first events in embryology occur at the time of conception, or fertilization of the ovum by a spermatozoon. It is at this moment, or in the first few subsequent cell divisions, that the chromosomal constitution (karyotype) is established. *The normal human cell contains 46 chromosomes (usually written 46,XY or 46,XX), 23 of which are provided by the maternal gamete (ovum) and 23 by the paternal gamete (sperm). The future individual's genotypic sex is now established as an X chromosome, is provided by the ovum and either an X or a Y chromosome by the sperm.* The presence and expression of the SRY gene, the testis-determining factor located on the Y chromosome, but rarely translocated to one of the other chromosomes, results in maleness.[1,6,7] In the absence of this locus, femaleness is likely to develop. Other non-Y-linked genes involved in sex determination have been found by genetic analysis of XY sex-reversed patients whose phenotype could not be explained by mutations in the TDF gene.[7] In the presence of SRY, the bipotential gonad progresses toward testis organogenesis.[6] SRY expression in Sertoli cell precursors activates downstream effectors, such as SOX9 (SRY-related HMG-box 9), which directs Sertoli cell proliferation and organization.[6] Much less information is known regarding the genes involved in ovarian organogenesis.

It is presumably at conception, as well, that certain other genitourinary abnormalities related to the individual's karyotypic constitution are determined. For example, many of the disorders of sexual development (DSDs) are determined at this time, either as deletions of chromosomes (e.g., Turner syndrome, 45,XO)[8] or as extra chromosomes (e.g., Klinefelter syndrome, 47,XXY).[9] The genital abnormalities of the Aarskog–Scott syndrome are also determined at this moment, as they are carried as an X-linked recessive trait.[10] Many of the trisomy syndromes include abnormalities of the genitalia and of the urinary tract as part of their spectra of expression.[11] The syndrome of Wilms' tumor and aniridia is related to a chromosomal abnormality (deletion of the short arm of the 11th chromosome).[12] Many other urinary abnormalities are probably also determined at this time, although the exact nature of many of these processes is as yet unknown. Others that seem to be familial in nature include duplication anomalies,[13,14] vesicoureteral reflux (VUR),[15,16] congenital ureteropelvic junction (UPJ) obstruction,[17] renal agenesis and dysplasia,[18] and hypospadias.[19] Some have been grouping seemingly different abnormalities in a kindred into one classification—congenital abnormalities of the kidney and urinary tract (CAKUT)—and feel that they are genetically and causally related. Some abnormalities are inherited as autosomal dominant traits (e.g., autosomal dominant [adult] polycystic disease), while others (e.g., autosomal recessive [infantile] polycystic disease and adrenogenital syndrome) are autosomal recessive traits.

Early embryonic life can be negatively influenced by teratogens such as heat, viruses, and drugs (Table 14.1). Maternal hyperthermia can induce neural tube defects in the embryo. Hyperthermic states have also been associated with hypothalamic lesions, leading to micropenis.[11] Some viruses, when they infect the mother, may produce congenital abnormalities in the fetus. Urologic abnormalities appear more frequently than normal in the congenital rubella syndrome.[20] It is well known that maternal ingestion of drugs can affect the developing fetus. Progestational agents may masculinize a female fetus.[21] The maternal production of androgens by ovarian tumors can also masculinize a female fetus. Maternal use of oral contraceptive pills has been theorized to be associated with the development of hypospadias.[22] Use of angiotensin-converting enzyme (ACE) during pregnancy has been associated with renal dysplasia, probably due to the drug's deleterious effects on the developing renal vasculature.[23] The fetal alcohol syndrome, on occasion, includes urinary abnormalities.[24] In addition, the use of anticonvulsant medications during pregnancy has been associated with genitourinary abnormalities in the fetal

TABLE 14.1 Genitourinary tract teratogens

Teratogen	Potential Genitourinary Defect
Maternal hyperthermia	Micropenis
Rubella virus (congenital rubella)	Hypospadias, cryptorchidism
Progestational agents	Ambiguous genitalia
Oral contraceptives	Hypospadias
ACE inhibitors	Renal dysplasia
Ethanol (fetal alcohol syndrome)	Hypospadias, hydronephrosis
Anticonvulsants	Hypospadias, ambiguous genitalia, cryptorchidism
Cocaine	Eagle–Barrett syndrome, hypospadias, hydronephrosis

hydantoin syndrome[25] and the fetal trimethadione syndrome.[26] Maternal use of recreational drugs, such as cocaine and methamphetamine, has been associated with anomalies of the genitourinary system, including Eagle–Barrett syndrome and hypospadias.[27] Excessive vitamin A ingestion during the first trimester of pregnancy has been reported to increase the risk for the development of genitourinary abnormalities.[28] In addition, physical forces (e.g., compression of the fetus within the uterus secondary to oligohydramnios) can induce permanent physical changes in the fetus, even at a relatively late stage of development. These are termed "deformation syndromes," of which Potter's syndrome is thought to be one.[29]

Increasingly, disorders of embryogenesis can be detected on prenatal ultrasound. For this reason, the evaluation of pediatric urological patients often begins in the fetal stage. Urologists are often consulted before the child is born to counsel parents on the prognosis and treatment of the abnormality that has been detected. Moreover, potential parents sometimes seek preconception guidance from specialists regarding genetic risks to a potential fetus. These families are interested in ways to detect and/or quantify these risks and to understand ways to minimize them. Answers to many of these questions are forthcoming as results of detailed molecular and genetic studies continue to provide clinical information.

Recent work on the Sonic hedgehog (SHH) signaling pathway represents an exciting new molecular mechanism important in genitourinary tract development. The hedgehog (HH) gene was initially implicated in controlling segment polarity in fruit fly embryos.[30] SHH, the best-studied homologue of HH, has recently been shown to play a functional role in genitourinary tract morphogenesis and differentiation.[30,31] As we continue to expand our understanding of these cellular and molecular mechanisms involved in genitourinary tract development, clinical applications and improvement in genetic counseling will surely follow.

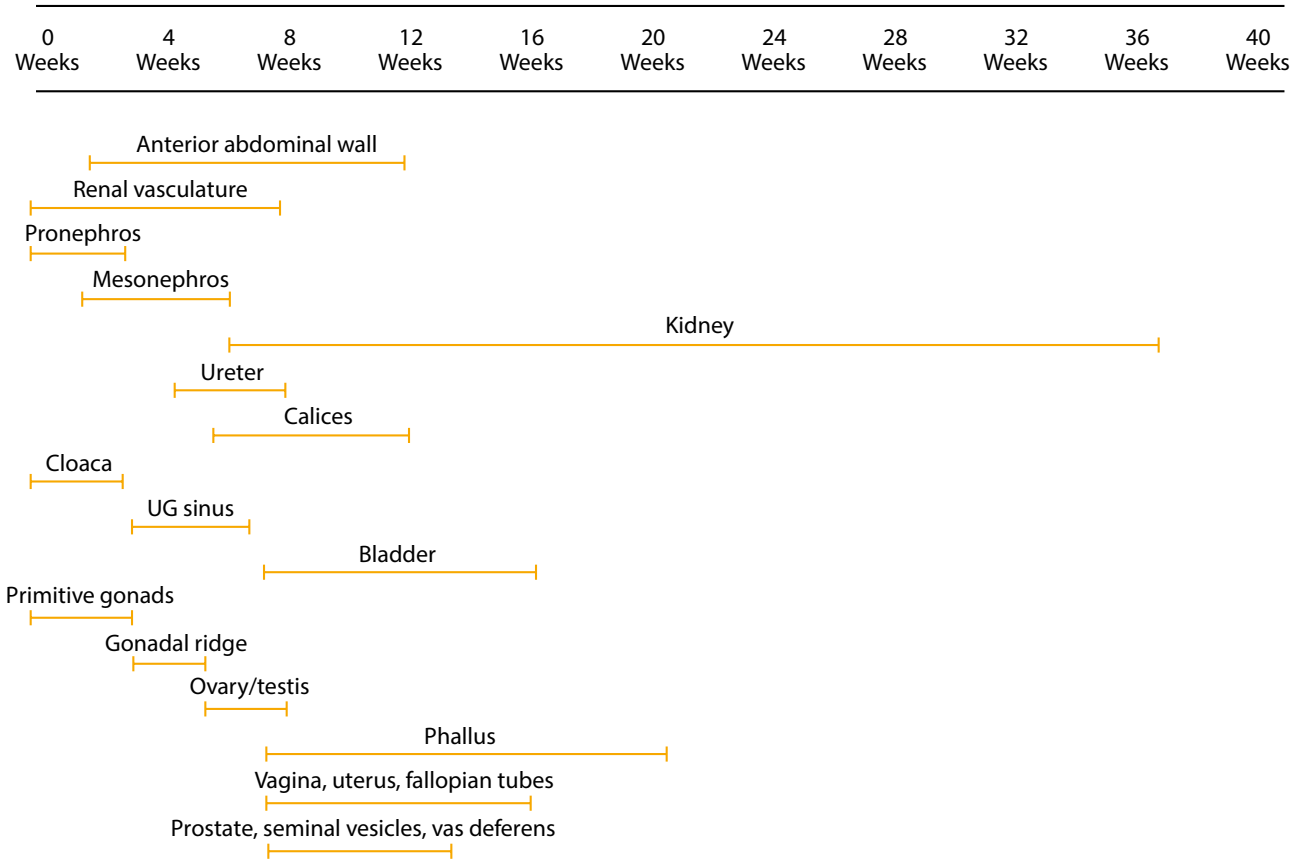

FIGURE 14.1 Genitourinary tract developmental timeline.

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Section 2

The Adrenal

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CHAPTER 15

Adrenal or Suprarenal Gland Development

Steven E. Lerman, Irene M. McAleer, Alan L. Kaplan, and George W. Kaplan

The developing fetal adrenal gland plays an essential role in intrauterine homeostasis, fetal organ maturation, preparation for extrauterine life, and parturition.[1]

The adrenal or suprarenal glands are located near the superior poles of the normally placed kidneys and contain two distinct different functioning areas of tissue, the cortex and the medulla. Although anatomically very close, the cortex and the medulla arise from two different and distinct areas. *The adrenal medulla is derived from migrating ectodermal neural crest cells. The cortex develops from the primitive mesoderm medial to the urogenital ridge, starting about the fourth gestational week.* By the sixth week, the cortex is apparent as an aggregation of mesenchyme on either side of the root of the mesentery and the developing gonad. At this time, nerve fibers, which the developing medullary cells will traverse, penetrate the developing adrenal cortex. The cortex develops two distinct areas by the eighth gestational week. The central area or the fetal zone is laterally and centrally located, while a thin rind develops on the outer aspect of the adrenal as the ultimate definitive adult cortex. The fetal zone comprises about 85% of the developing fetal adrenal gland.[2] The definitive cortex begins to differentiate into hormone-producing zones, the zona glomerulosa and the zona fasciculata, late in gestation. Most of the developing proliferation during the latter part of gestation is in the peripheral cortex region. The zona reticularis does not become apparent until about the end of the third year of life (Figure 15.1). The zona glomerulosa or outermost layer of the definitive cortex produces aldosterone. The zona fasciculata and zona reticularis form a unit after the reticularis develops in early childhood. The zona fasciculata produces the glucocorticoid hormones, while the zona reticularis produces the sex or androgen hormones.

Adrenal arterial circulation develops from developing descending aorta; several arteries feed the adrenal cortex and infiltrate from the cortex to the medulla in a fine network of vessels. A central vein drains each adrenal gland. Angiogenesis, the formation of new capillaries from preexisting blood vessels, is essential for the rapid growth of the fetal adrenal typically occurring in midgestation. Because of the required delivery of steroid precursors during development, the fetal adrenal requires extensive vasculature. Ishimoto et al. found through immunostaining of pathologically obtained fetal adrenal glands that the primary site of angiogenesis is in the periphery of the developing gland. They found that angiogenic factors (Ang2, VEGF-A, and FGF-A) were locally produced and induced fetal adrenal angiogenesis. Proliferation of the vascular endothelial cells appears to be limited to the periphery of the definitive zone during midgestation.[1]

The adrenal glands increase in size from around the second to third month of gestation, growing from about 5 to 80 mg, and are much larger than the adjacent kidney for much of development and remain large even after birth (Figure 15.2). Most of this mass is due to the fetal cortex and the developing definitive adult cortex; the adrenal medulla is quite small until after birth. The adrenals lose most of their mass shortly after birth, with about one-third of the weight lost in the first 2–3 weeks after birth (Figure 15.3). The loss in mass is due to the involution of the large fetal cortex zone. The original weight is not regained until about the end of the second year of life.

The adrenal cortex arises from the common adrenogonadal precursors in the intermediate mesoderm. The rudimentary adrenal gland fetal zone expresses 17-α-hydroxylase (CYP17), which is a steroidogenic enzyme. During development, the fetal zone expresses cholesterol side-chain cleavage exzyme (CYP11A) and CYP17, which drive the fetal adrenal to produce primarily dehydroepiandrosterone (DHEA) and its derivatives. Ultimately, the adrenal cortex encapsulates when the neural crest cells migrate to form the adrenal medulla.[3] Some primitive adrenocortical cells may migrate beyond the normal suprarenal location during formation. Accessory adrenocortical rests may be found adjacent to the celiac plexis, in the broad ligament, near the ovarian or spermatic vessels or around the kidneys or uterus. Rarely, these rests may be found near other abdominal organs or even the lungs or spinal nerves, or in the brain. Some of these rests may be responsible for Cushing's disease or malignant degeneration.[4]

The medulla arises from the neural crest cells of the primitive sympathetic nervous system. The migrating neuroectodermal cells differentiate into neuroblasts, ultimately forming the paravertebral and para-aortic sympathetic ganglia, and pheochromoblasts, which form catecholamine-secreting chromaffin cells. The chromaffin cells are found throughout the adrenal medulla and the sympathetic chain in the fetus, but the extra-adrenal sites generally involute after birth. Persistent extra-adrenal tissue can be found near the origins of the celiac and mesentery arteries; another site, the organs of Zuckerkandl, is located near the inferior mesenteric artery and may be prominent during the first year of life, after which this

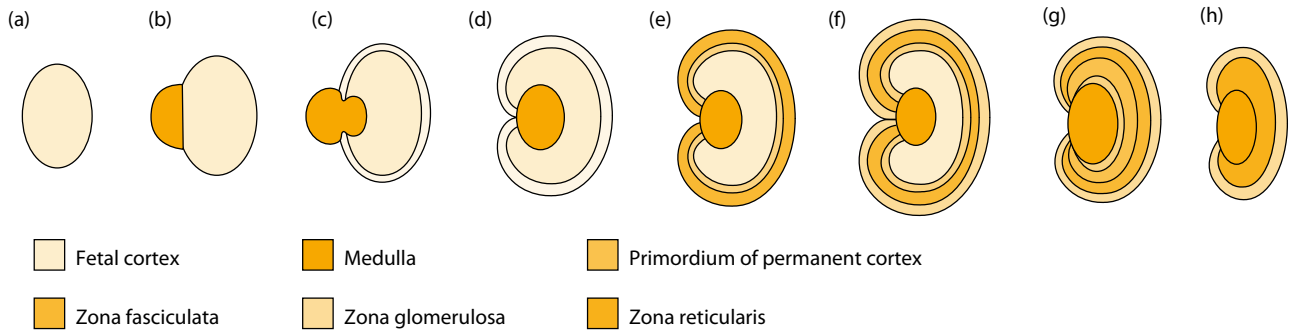

FIGURE 15.1 Schematic drawings of the development of the suprarenal gland. (Adapted from Moore KL, Persaud TVN. *The Developing Human: Clinically Oriented Embryology*, 7th edn. Philadelphia: Saunders, 2003.)

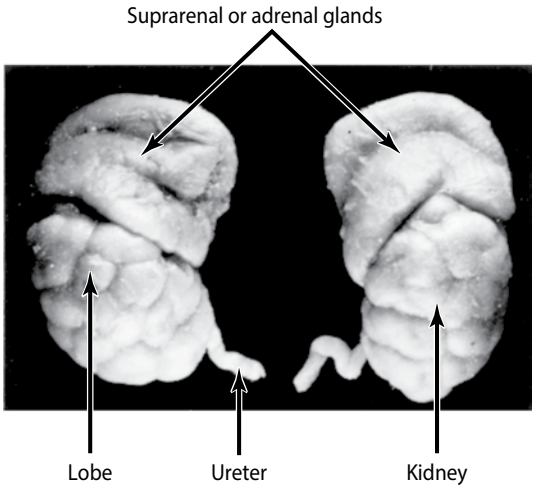

FIGURE 15.2 Photograph of kidneys and adrenal glands of a 28-week fetus. (Adapted from Moore KL, Persaud TVN. *The Developing Human: Clinically Oriented Embryology*, 7th edn. Philadelphia: Saunders, 2003.)

tissue generally involutes but may be a site of extra-adrenal pheochromocytoma development later in life.

The fetal adrenal cortex produces large amounts of dehydroepiandrostenedione sulfate (DHEA-S) after the first trimester. Induction of DHEA and DHEA sulfate occurs when the fetal zone expresses the 450C17 enzyme. Steroidogenesis is regulated by steroidogenic factor-1 (SF-1) and dosage-sensitive sex reversal-adrenal hypoplasia congenita (DAX-1) found on a critical region on the X chromosome gene 1. DAX-1 is a negative regulator of SF-1, which is an activator of steroid hormone production.[2] Steroidogenesis during the second trimester occurs in the fetal zone, while it is absent in the definitive zone at the same time period. DAX-1 is found during the second trimester in both the nucleus and the cytoplasm in the inner and outer fetal gland, as it is found on immunochemical staining of pathologically obtained fetal adrenal glands. Battista et al. found while staining this tissue that the extracellular matrix plays a critical role in modulating cell proliferation, apoptosis, and steroidogenesis. The adrenocorticotropic hormone (ACTH) stimulates the nucleus of the fetal zone cells activating DAX-1-negative modulation of fetal adrenal steroidogenesis. The stimulation activates the highly proliferative definitive zone, whereas the stimulation does not cause fetal zone cells to proliferate.[2] The outer cortex is believed to produce cortisol after about 28 weeks' gestation, although cortisol can be measured as early as the eighth gestational week.

Kim et al. also found that DAX-1 was expressed in the fetal zone initially, but when the definitive zone arises, it is found to be active in the subcapsular zone of the adrenal gland, as it stimulates cell growth through regulation by orphan nuclear receptor (Sf1).[5] They propose that DAX-1 is activated to stimulate cell growth by glucocorticoids released by the differentiated cortical cells, whereas ACTH stimulation inactivates DAX-1 while stimulating steroidogenesis by the adrenal cortical

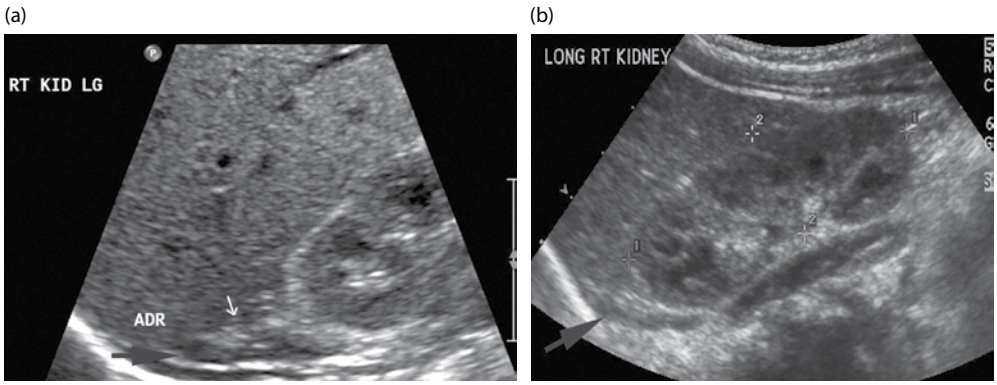

FIGURE 15.3 Ultrasound images of adrenal gland in 2-week-old boy (a) and at 4 months old, demonstrating involution of the gland size after the first month of life (b).

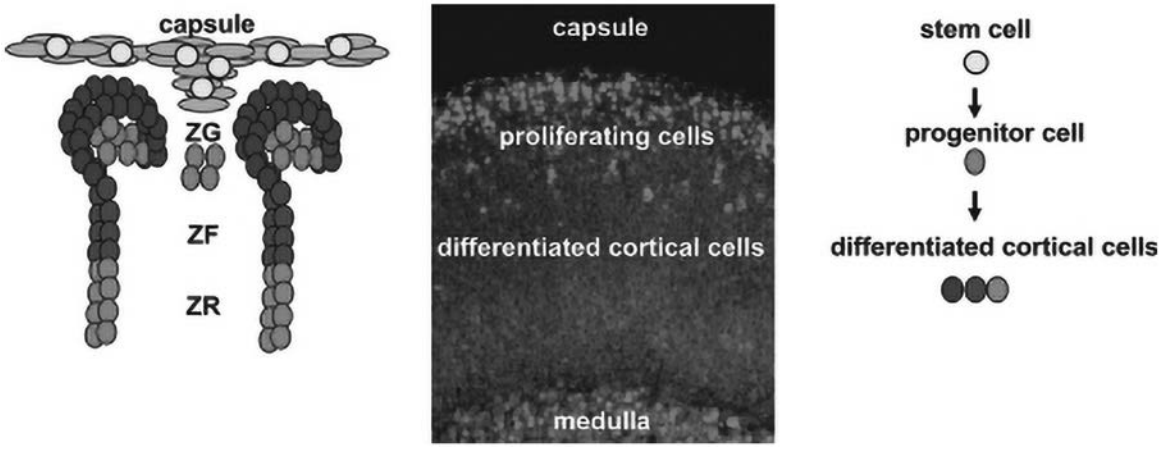

FIGURE 15.4 Cellular organization of the developing adrenal cortex. (Adapted from Kim AC et al. *Endocr Rev* 2009;30(3):241–63.)

cells.[5] The developing adrenal gland also produces large amounts of inhibin-α, specifies adrenal cell development, and prevents development of ovarian-like tissue, as both tissues develop from the same band of adrenogonadal primordia (Figure 15.4).

The definitive zone cells located in the periphery are nonsecretory until the second trimester. These cells proliferate rapidly and move into the outer layers of the fetal zones centripetally, and then differentiate into steroid-producing cells. By the end of the second trimester, a third transitional zone is found between the first two zones.[6,7] Angiotensin II (AngII) is expressed through two subtypes in the fetal adrenal gland: the AT2 subtype is found in the fetal zone, and AT1 is found in the definitive zone after the 16th week of pregnancy. AT2 regulates apoptosis in the fetal zone during adrenal development. The development of the fetal adrenal gland depends on proliferation at the periphery in the definitive zone and apoptosis in the central fetal zone. Chamoux et al. found that primary extracellular matrix in the developing adrenal gland composed of collagen IV increased cell responsiveness to ACTH and AT1 receptor effects of AngII, while laminin reduced cell responses to ACTH and AT2.[6,7] Stimulation of cortisol secretion by ACTH is enhanced in the fetal zone due to large volumes of collagen IV in that area, as well as also being found in the smaller, more compact, definitive zone. They found laminin mostly concentrated in the periphery and the fibronectin mostly located in the central zone. These extracellular matrix proteins enhanced peripheral cells of the developing outer cortex to proliferate while maintaining central fetal zone cells for further steroid secretion from its cells.[6,7]

The fetal hypothalamic–pituitary–adrenal (HPA) axis is an example of reciprocal induction where the development, differentiation, and maturation of vital organ systems (lungs, brain, and liver) for immediate postnatal survival and parturition are hinged on interactions between the organs of the developing endocrine axis.[8] The hypothalamus releases corticotrophin-releasing hormone (CRH) as early as 8–12 weeks' gestation. CRH regulates the growth of the pituitary corticotrophins (adrenocorticotrophin and ACTH proopiomelanocortin [POMC]) and mRNA expression, as well as acting as a potent vasodilator of the fetoplacental circulation, and potentiates local prostaglandin and oxytocin function for uterine contractions during labor.[9] Placental estrogens facilitate conversion of fetal cortisol to inactive cortisone, which causes negative feedback on the fetal HPA axis, resulting in increased POMC mRNA, ACTH, adrenal cortisol, and DHEA-S production. Interestingly, increased fetal adrenal glucocorticoid stimulates the release of placental CRH, which increases the stimulation on the fetal pituitary to increase ACTH release, which then causes the adrenal to produce more cortisol, which is critical for the transition from fetal life to extrauterine life at the end of gestation. The importance of this upregulation of cortical hormone for transition to infant well-being and survival after delivery has been shown in outcome studies of extremely preterm small

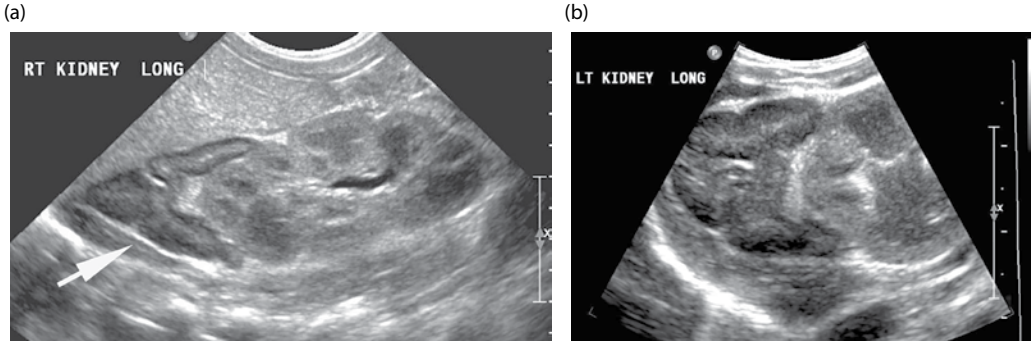

FIGURE 15.5 Adrenal glands in infant girl with CAH (sizes at this age are similar to those of newborns not affected by CAH).

neonates who were delivered prior to attaining the normal adrenal developmental milestones in utero.[9,10]

A serious and potentially life-threatening condition is congenital adrenal hyperplasia (CAH), which is a group of autosomal recessive disorders, the most common of which is caused by a mutation of the cytochrome P450 21-hydroxylase (CYP21) gene. This mutation causes deficient production of the cortical enzymes necessary for producing corticosteroids or mineralosteroids needed for life. Other forms of CAH are not as common, and the etiology of the defects is also not as well known. The decreased cortical hormone production stimulates the fetal pituitary to produce more ACTH, which then causes the adrenal to enlarge and produce more adrenal androgens and androgen precursors that do not require 21-hydroxylation. The excess androgen activity will cause masculinization of female fetuses. The excessive hormone production must occur within the first trimester to produce the masculinization changes that can only take place during early genital development (Figure 15.5).[11,12]

It is believed that adrenocortical carcinomas that develop later in life are mostly monoclonal in origin. Certain hereditary adrenocortical carcinoma syndromes, such as Beckwith–Wiedemann syndrome (BWS), familial adenomatous polyposis (FAP), and Li–Fraumeni syndrome, are thought to arise because of problems with regulation of cell development and apoptosis. It has been found in BWS and FAP that the genes IGF-II and IGF-I are critical for normal progenitor development.[5]

During the pregnancy, especially during the second and third trimesters, levels of DHEA and DHEA-S are very high, as are the levels of 3β-hydroxysteroid dehydrogenase. At birth, the fetal adrenals undergo massive involution, losing about 50% of their mass in the first month of life. Rapid decline in androgen secretion follows the decreasing postnatal size of the adrenal gland. Ben-David and colleagues found that DHEA-S, cortisol, and androstenedione levels decrease with birth, as does the rapid postnatal involution of the fetal adrenal gland, regardless of gestational age.[13] This involution, which is not dependent on fetal age at birth, implies that parturition itself is responsible for fetal adrenal involution and maintenance of a normal functioning adrenal gland for the neonate after birth. Fetal adrenal production of androgens depends on 17-hydroxylase activity. Parturition with accompanied involution of the fetal adrenal shows a marked drop in 17-hydroxylase activity. Any rise in androgen production in boys is due to gonadal activity after birth.[13]

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CHAPTER 16

Radiological Assessment of the Adrenal

Kourosh Afshar, Douglas H. Jamieson, and Andrew E. MacNeily

INTRODUCTION

Diagnostic imaging is an essential part of the investigation of adrenal disorders. Modalities such as ultrasound, MRI, and computed tomography (CT) scan have replaced older techniques, such as intravenous urography and angiography. In this chapter, we discuss the imaging characteristics of the more common childhood adrenal abnormalities (Table 16.1).

SOLID MASSES OF THE ADRENAL

Neuroblastoma

If a solid adrenal mass is encountered when a child is imaged, neuroblastoma must always be considered. These are malignant tumors originating from neural crest cells with a peak age incidence of 2.5 years. They arise from the adrenal medulla in 40% of cases, the remainder being extra-adrenal in origin. Although they can be detected incidentally at the time of imaging for other indications, neuroblastoma usually presents as a large abdominal mass and is metastatic in 70% of cases at the time of presentation.[1]

Calcification, which is amorphous and speckled, is seen on up to 50% of plain abdominal radiographs and 80% of CT scans.[2] On ultrasound, tumors are solid and heterogeneously echogenic with occasional hypoechoic areas.[3] Ultrasound is a useful method for follow-up.

Cross-sectional imaging (CT or MRI) depicts a large irregular mass and punctuate calcification with or without enlarged lymph nodes or visceral metastases.[4] Neuroblastoma tends to cross the midline and encase vascular structures. It displaces the kidney laterally and inferiorly (Figures 16.1 and 16.2). These features are helpful to differentiate neuroblastoma from a large Wilms' tumor.[5] On CT, areas of low attenuation often represent cystic necrosis or hemorrhage (Figures 16.3 and 16.4a,b).[5] On MRI, the mass has low or intermediate signal intensity on T1-weighted images and high intensity on T2-weighted images.[6] CT- or MRI-based myelograms are useful in selected cases to assess the extent of intraspinal extension, presenting as a dumbbell-shaped tumor (Figures 16.5a and b and 16.6a–c).[7] Some authors prefer MRI for cross-sectional imaging for better delineation of hepatic metastasis, vascular involvement, and intraspinal extension.[8] Iodine^{132} or I^{131} or I^{123} metaiodobenzylguanidine (MIBG) scintigraphy demonstrates uptake by the primary tumor and any metastatic sites, such as bone.[9,10] However, MIBG has up to 30% false-negative results in diagnosing primary tumors and is less sensitive than 99m technetium methylenediphosphonate (^{99m}Tc MDP) at diagnosing bony metastases. In practice, the 2 tests are used to complement each other.[5,11] A recent study concluded that both CT and MRI have poor accuracy for estimating local extension, but when either modality is combined with ^{99m}Tc MDP scintigraphy, they are equally useful in diagnosing stage 4 disease, with an accuracy of 90%.[12]

TABLE 16.1 Differential diagnosis of antenatally detected adrenal masses

Adrenal hemorrhage
Neuroblastoma
Renal duplication anomaly
Pulmonary sequestration
Enteric duplication

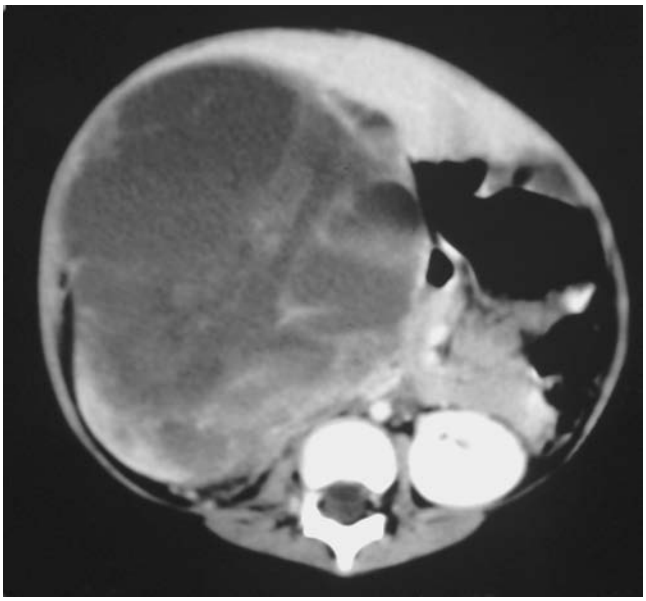

FIGURE 16.1 Contrast-enhanced CT demonstrates a large heterogeneous mass with areas of nonenhancing low density. It is difficult to separate a mass arising from the upper pole of the right kidney from an adrenal mass. The tumor renal interface is indistinct.

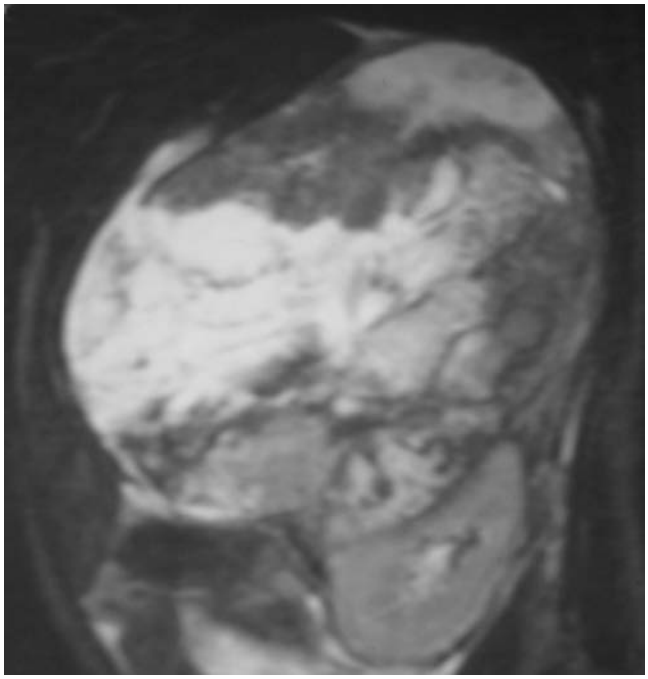

FIGURE 16.2 Sagittal T2-weighted MR image clearly demonstrates a tumor mass displacing the right kidney inferiorly, confirming adrenal mass. The mass has large areas of increased T2 signal intensity corresponding to the low-density areas on CT (Figure 16.1). Areas of tumor necrosis or old areas of hemorrhage are suspected.

FIGURE 16.3 Contrast-enhanced CT in a 4-year-old child presenting ill, with weight loss and a hard abdominal mass. There is a large mass in the left adrenal or retroperitoneal location. Dense areas of opacity indicate calcification. The mass enhances poorly and inhomogeneously. Lymphadenopathy surrounds the aorta, displacing it away from the vertebral body. Histology confirmed neuroblastoma.

Ganglioneuroma and Ganglioneuroblastoma

These benign tumors arise from sympathetic ganglions and represent a more differentiated form of neuroblastoma. On CT, they manifest as an oval, discrete mass

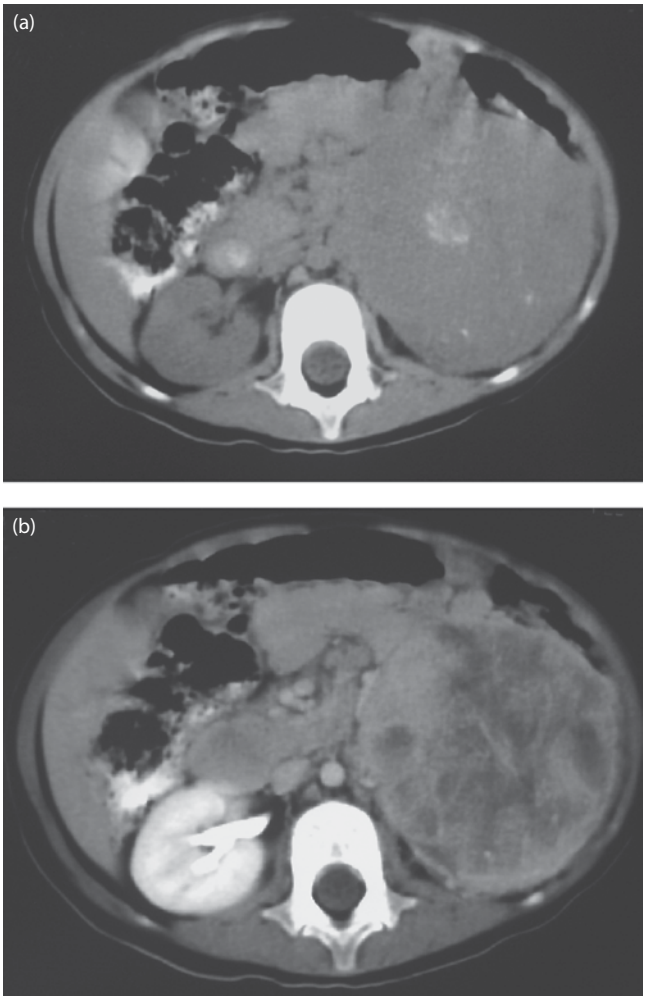

FIGURE 16.4 (a) Nonenhanced CT demonstrates a large left neuroblastoma mass with calcification. Note that the nodal spread to the right renal hilar region also has calcification. (b) Contrast-enhanced CT slightly inferior to (a) shows marked inhomogeneity of enhancement.

with variable enhancement. Calcification that is usually not as extensive as in neuroblastoma is seen in 20% of cases. On MRI, the mass has a low-intensity signal on T1 and a high-intensity one on T2 images, with a characteristic whorled appearance.[13] Ganglioneuroblastoma is an intermediary tumor of sympathetic tissue containing both benign and malignant elements. It has variable imaging features, depending on the composition of the tumor.[13]

Ganglioneuromas are generally more homogeneous with a lower T1 intensity than the liver.[14]

Pheochromocytoma

Also a tumor of neural crest cells, pheochromocytoma tends to occur in older children compared with neuroblastoma. The main presentation is a headache due to hypertension.[15] The only reliable criteria for malignancy are local invasion and metastasis. On ultrasound, the tumor is seen as a hypoechoic mass, occasionally containing small cysts. Generally, CT and MRI are both highly (>90%) sensitive

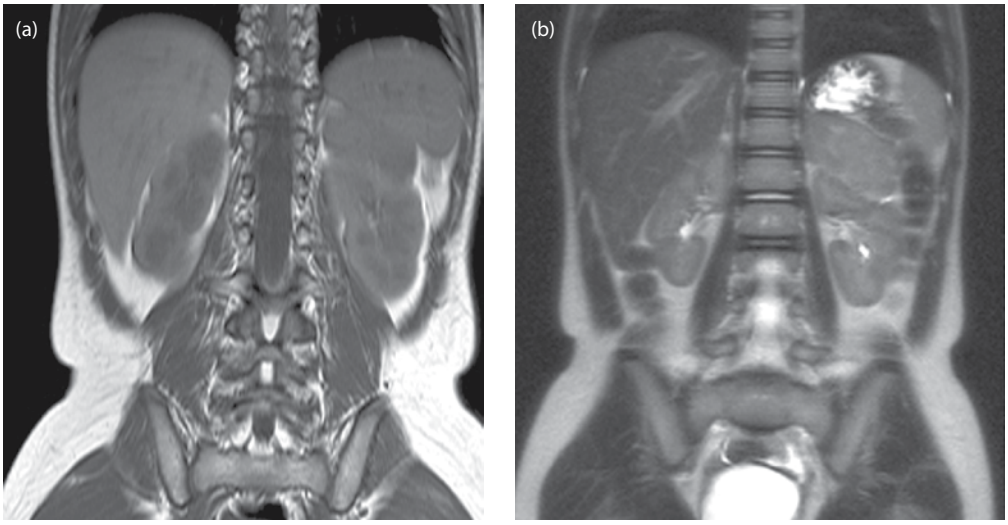

FIGURE 16.5 Coronal T1 MR image (a) and coronal T2 MR image (b) demonstrate a left adrenal mass that is homogenous and has soft tissue signal characteristics. This is usual for a smaller neuroblastoma, where tumor necrosis and hemorrhage are less encountered. Note that MR can easily miss calcification, although this has little impact on diagnosis.

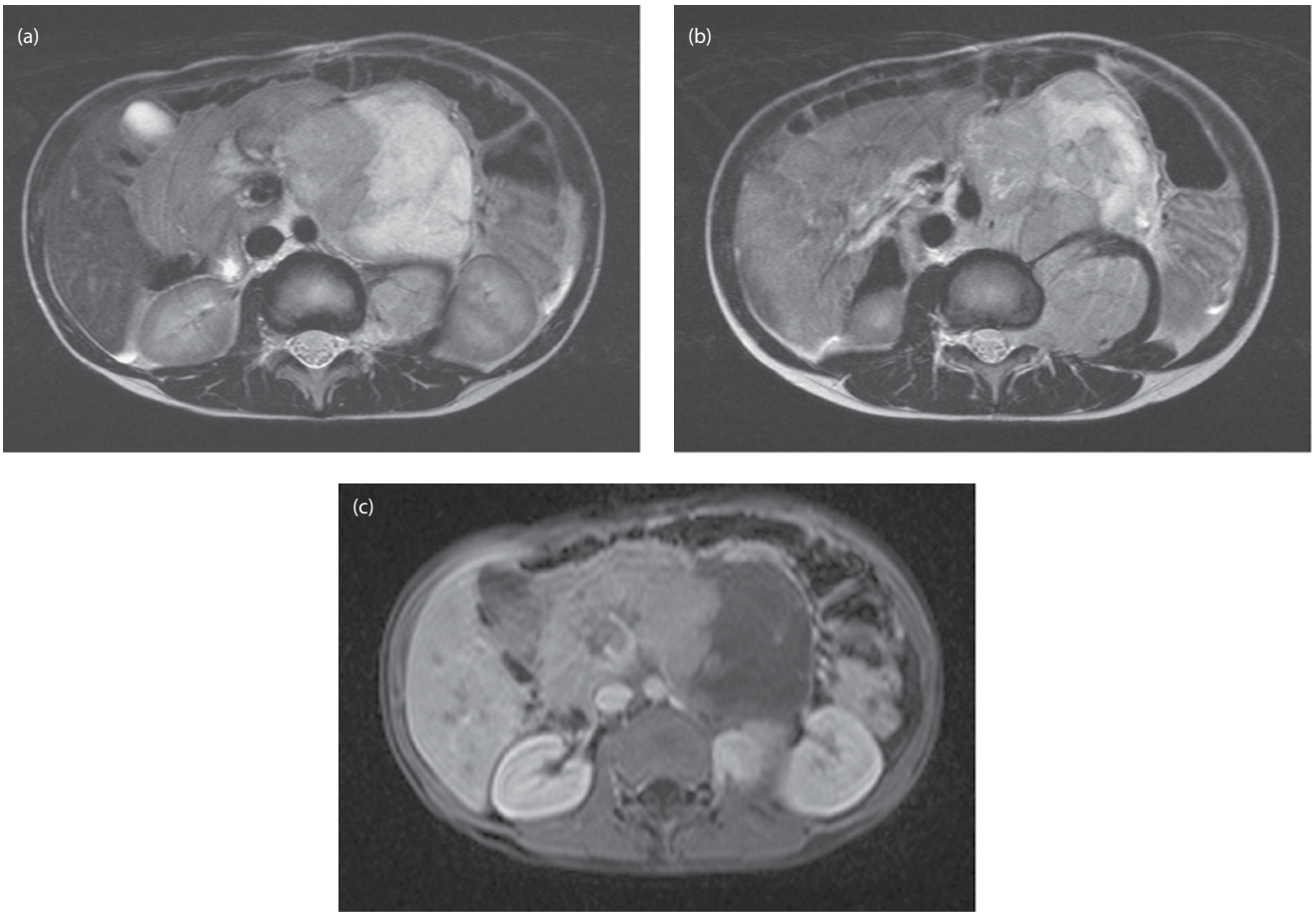

FIGURE 16.6 Axial T2 MR image (a and b) and gadolinium-enhanced fat-saturated T1-weighted MR image (c). Large heterogeneous tumor mass crossing the midline is well delineated. The extensive left-sided area of increased T2 signal intensity shows no contrast enhancement and suggests tumor necrosis. It would be important to direct biopsy away from this area to obtain appropriate diagnostic information. Note also the tumor encroachment on the left-sided neural foramen (b). Evaluation of tumor extent into the spinal canal is superbly imaged by MRI.

and specific in diagnosing and staging pheochromocytomas, but because of the possibility of a hypertensive crisis, induced by the iodinated contrast material, some authors prefer MRI as the first choice for cross-sectional imaging. However, at least one study has demonstrated that nonionic contrast agents are safe in the setting of a confirmed pheochromocytoma.[16] On unenhanced scans, tumors are isodense to the surrounding soft tissue but enhance intensely following IV contrast.[17] MRI generally characterizes these tumors as possessing low signal intensity on T1-weighted images and a characteristic marked increased signal intensity on T2 images secondary to their high vascularity.[18] More recent studies have shown variability in T2 signal, with up to 30% of cases having low signals.[13] MIBG scans have a sensitivity and specificity of 90% in detecting functioning tumors, but without the anatomic resolution provided by cross-sectional imaging.[4,19] MIBG combined with single-photon emission computed tomography (SPECT) is useful in detecting equivocal cases.[20]

Cortical Neoplasms

These are rare tumors of childhood mostly associated with endocrine syndromes.[21] In the absence of metastasis, the distinction between adenoma and carcinoma is very difficult, even with a histological study of the removed tumor.

On ultrasound, these tumors present as round or ovoid masses, commonly lobulated. They may be hypo- or hyperechoic, and the larger tumors are inhomogeneous.[22,23] On CT, they manifest as circumscribed and heterogeneous masses. The criteria used in adults to differentiate between adenoma and carcinoma, such as unenhanced densiometry and size, have not been studied adequately in children. On MRI, cortical neoplasms have intermediate-intensity T1 and high-intensity T2 signals.[24] Chemical shift MRI has been shown to be a reliable modality for differentiating adenomas from malignant lesions in adults.[25]

Myelolipoma

This rare benign tumor is composed of adipose and bone marrow elements. The diagnosis is made based on the demonstration of macroscopic fat on CT or MRI.[26] On CT, areas of macroscopic fat have a low Hounsfield unit (<30). On MRI, fat is characterized by a hyperintense T1 signal that reduces with fat suppression.

Adrenal Metastases

Metastatic lesions presenting as an adrenal mass are rare in children. The likelihood of adrenal metastasis with no history of previous cancer is extremely low.[27]

The imaging criteria to differentiate primary adrenal adenomas from secondary tumors, as described in adults, such as attenuation values of more than 10 Hounsfield units or signal loss of less than 20% in chemical shift MRI,[28] have not been studied in children. Fluorodeoxyglucose positron emission tomography–computed tomography (FDG PET-CT) has been shown to have an accuracy of more than 90% to diagnose adrenal metastases.[29]

Renal Lesions

Lesions in the upper pole of the kidney should be included in the differential diagnosis of an adrenal mass. Wilms' tumor, renal cell carcinoma, and a hydronephrotic upper-pole moiety of a duplicated system can all masquerade as a primary adrenal mass.

CYSTIC MASSES OF THE ADRENAL

These lesions are usually unilateral and asymptomatic. They may be classified as pseudocysts or endothelial, epithelial, or parasitic cysts. Pseudocysts are formed following hemorrhage into normal or abnormal adrenal tissue. Examples include bleeding into or necrosis of a neuroblastoma or adrenal carcinoma. Calcification is common. Endothelial cysts are the most common category in some series.[30] They may have a vascular or lymphatic origin, and are lined by the corresponding endothelium.[31] Epithelial cysts may be true glandular cysts or embryonal or cystic adenoma.[32] Hydatid cysts constitute the majority of parasitic cysts described in the literature.[33] Typically, cysts are hypoechoic on ultrasound. They possess low intensity on T1-weighted MRI and high intensity on T2-weighted MRI. Treatment of adrenal cysts depends on the underlying pathology and ranges from percutaneous aspiration of cysts containing water density fluid, to laparoscopic or open adrenalectomy for more complex lesions.[34]

ANTENATALLY DETECTED ADRENAL MASSES

With the advent of routine maternal fetal ultrasound, the detection of fetal adrenal masses is becoming increasingly common. Most of these lesions are detected in the third trimester, with the majority being cystic or cystic and solid in nature. Ultrasound is the modality of choice for initial and follow-up evaluation of these findings. In neonates, the normally large adrenal glands are clearly visualized and consist of a hypoechoic cortex and a thin echogenic medulla. The differential diagnosis for antenatally detected adrenal masses is shown in Table 16.2. The intensity of imaging and clinical management of these incidental findings must strike a balance between aggressive surgical intervention for a presumed malignancy and watchful waiting for a benign condition, or one that has a natural history of spontaneous involution.

In a retrospective study of 30 prenatally diagnosed adrenal masses reported from Paris, 13 (43%) were ultimately found to be neuroblastoma, with the remainder representing mainly adrenal hemorrhage with the rare pulmonary sequestration.[28] In a more recent series, 13 out of 18 prenatally diagnosed adrenal masses were neuroblastomas, mostly stage 1 (Figure 16.7).[35] Antenatally detected neuroblastoma can be either cystic or solid. Of importance is the fact that MIBG scanning only provided a 70% sensitivity and a 55% negative predictive value for neuroblastoma in this population. Similarly, urinary catecholamines provided only 36% sensitivity and a 72%

TABLE 16.2 Imaging characteristics of pediatric adrenal masses

Adrenal mass	Ultrasound	CT scan	MRI	Nuclear scan
Neuroblastoma	Solid mass, heterogeneous echotexture	Heterogeneous, low attenuation areas of hemorrhage or necrosis, calcification up to 80%	Heterogeneous signal on T1 and high signal on T2	MIBG avid in 70% 99 Tc MDP more accurate for bone metastasis
Ganglioneuroma	Solid oval or lobulated mass	Homogeneous attenuation lower than muscle, varying degree of enhancement	Homogeneous low signal on T1 and whorled appearance on T2 with varying degree of enhancement	MIBG may be positive
Pheochromo-cytoma	Solid tumor, possible cystic area	Intense enhancement with contrast, low attenuation areas of necrosis/hemorrhage	Low intensity T1, extremely high intensity T2 signal	90% MIBG avid
Adrenal cortical neoplasm	Lobulated solid mass	Heterogeneous attenuation	Low T1 and high T2 signal intensity	
Metastasis		Attenuation <10 HU	Signal drop <20% in chemical shift MRI	
Adrenal hemorrhage	Initially hyperechoic with gradual liquefaction	Initial high attenuation (50–60 HU) with no enhancement	Initially: Low signal T1 Intermediate (1–5 weeks): High signal T1 and T2 Late (weeks to months): Low signal T1 and T2	

Abbreviation: HU, hounsfield unit.

negative predictive value. Postnatal features suggestive of neuroblastoma include large size (>3 cm), homogenously solid nature, and growth on serial follow-up. Conversely, development of calcification in follow-up, shrinkage in size, or development of internal echoes suggests a resolving adrenal hemorrhage (Figure 16.8a and b).[36]

Although adrenal hemorrhage classically occurs in the first few days of life in association with neonatal sepsis or other stressors, it may be observed in the second or third trimester of pregnancy, and therefore clinical features alone are inadequate to determine a diagnosis.[37] It is the most common neonatal adrenal mass, and occurs on the right side in 70% of cases. This latter characteristic is thought to be secondary to adrenal compression between the liver and kidney anteriorly and the spine posteriorly.[38]

FIGURE 16.7 Contrast-enhanced CT scan confirmed the antenatal and postnatal detection of a left adrenal cystic lesion. Surgical removal confirmed the diagnosis of a pulmonary sequestration.

Early ultrasound of an adrenal hemorrhage depicts a hyperechoic mass. Over the initial few days, the hematoma gradually liquefies (Figures 16.9 and 16.10). Complete resolution takes up to 6 weeks with occasional calcification or pseudocyst formation.[39] CT and magnetic resonance (MR) scanning are necessary only in selected cases to determine whether blood is the sole component of a mass, a finding that most likely indicates a benign cause. Acutely, CT of an adrenal hemorrhage is manifested as a well or poorly defined mass with increased attenuation (50–60 Hounsfield units) that does not enhance with intravenous contrast (Figure 16.11 and Table 16.2). In the acute phase, MRI of hematomas demonstrates a reduced signal on T1-weighted images. Methemoglobin in the subacute phase (1–5 weeks) causes high signal on both T1- and T2-weighted images. Chronic hemorrhage (5 weeks to 10 months) demonstrates the gradual formation of low signal hemosiderin.[38,39]

For small antenatally detected lesions, an initial postnatal ultrasound, MIBG scan, and urinary catecholamines should be routine. If initial investigations are suggestive of a benign process, then monthly ultrasounds for the first 6 months suffice. Surgical removal is recommended for an increase in size, elevated urinary catecholamines, or failure of involution with observation.[40]

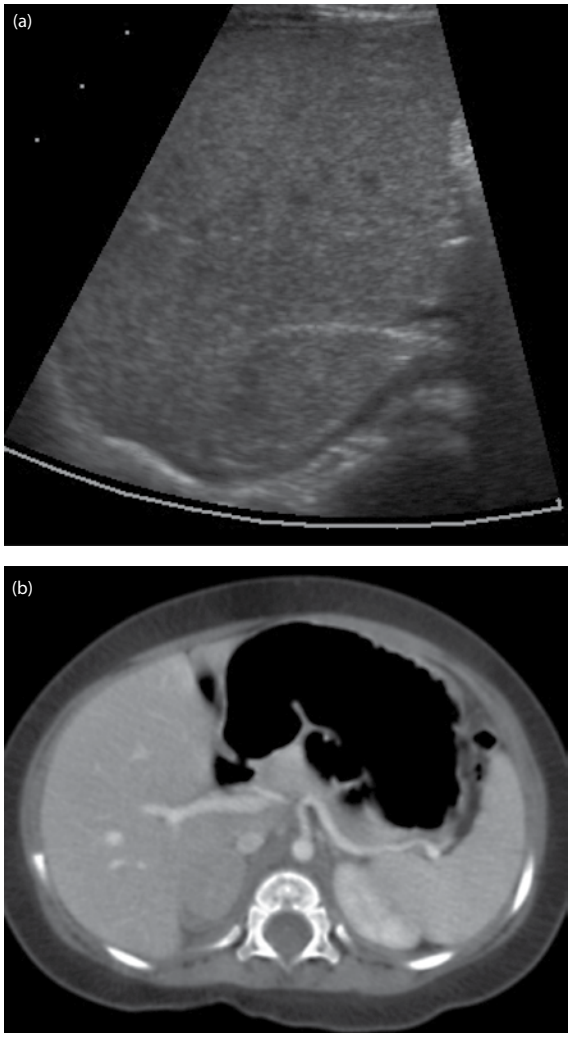

FIGURE 16.8 (a) Neonatal ultrasound performed in follow-up of an antenatally detected right surprarenal mass demonstrates a solid, fairly homogeneous right adrenal mass lesion. Serial images failed to demonstrate involution over the course of several weeks. (b) Subsequent contrast-enhanced CT shows a solid homogenous right adrenal mass confirmed to be neuroblastoma upon excision.

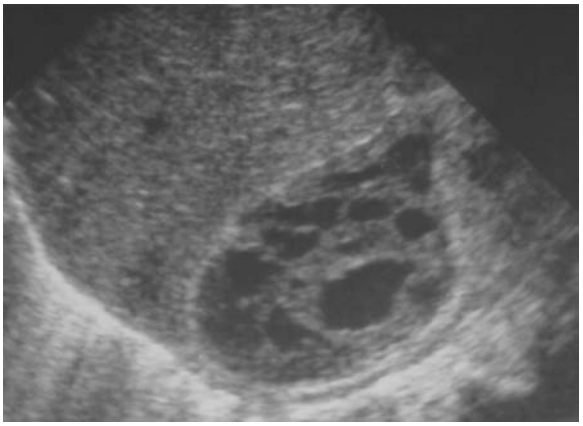

FIGURE 16.9 Ultrasound obtained in a 5-day-old neonate following traumatic delivery demonstrates a multiseptated right adrenal mass typical of an organizing hematoma.

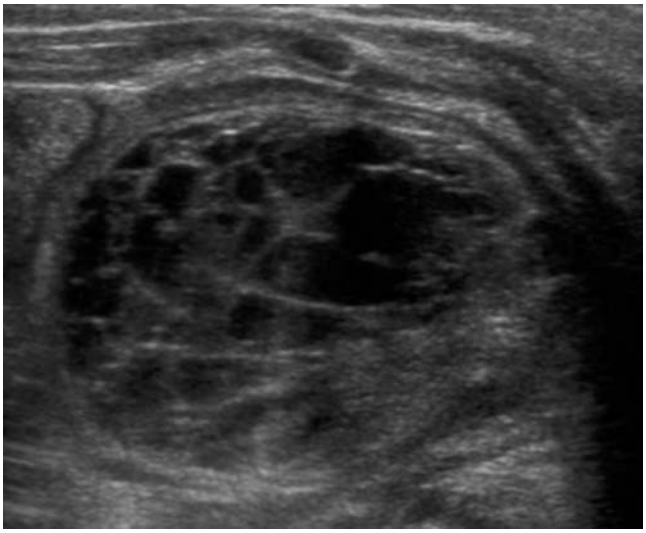

FIGURE 16.10 Sonogram on day 3 of life, requested to exclude renal anomalies in a patient with transposition of the great vessels. Unexpected but typical findings of a septated left adrenal hematoma. The incident causing the hematoma likely occurred in utero.

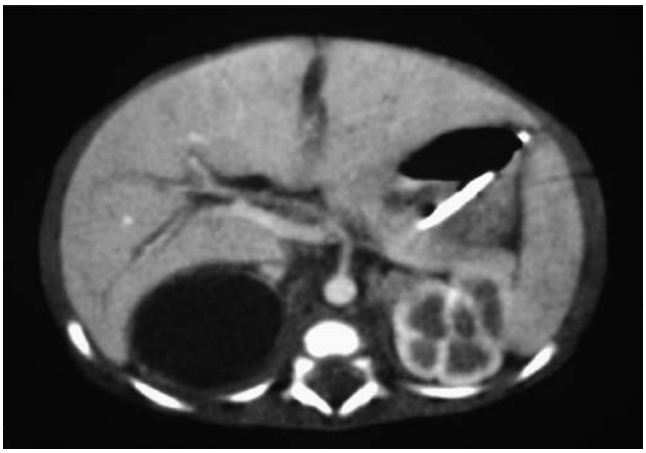

FIGURE 16.11 Contrast-enhanced CT on the same day as ultrasound in Figure 16.9. In the right adrenal location, a nonenhancing low-density mass typical of an adrenal hematoma is apparent. Note that the septations are not apparent on the CT.

CALCIFIED ADRENAL LESIONS

Adrenal calcification detected on abdominal imaging of a child has a broad differential diagnosis (Table 16.3), but it usually prompts investigations for a tumor, most commonly neuroblastoma.[39] The aforementioned affinity of neuroblastoma for skeletal tracer is independent of the presence of calcification, and its mechanism is unknown.[41] Ganglioneuromas and ganglioneuroblastomas can also calcify, and they are radiographically indistinguishable from neuroblastomas.

Granulomatous diseases often result in childhood adrenal calcification either unilaterally or bilaterally.[42–44] Distinguishing from the various granulomatous infections is impossible by imaging alone.

TABLE 16.3 Differential diagnosis of pediatric calcified adrenal masses

Neural crest tumors: Neuroblastoma[a] Ganglioneuroblastoma[a] Ganglioneuroma
Resolving hemorrhage[a]
Adrenal cortical carcinoma
Pheochromocytoma
Adrenal cortical adenoma
Granulomatous infection
Storage disorders: Wolman's disease Niemann–Pick disease
Myelolipoma

[a] Denotes most common findings.

Wolman's disease is an uncommon autosomal recessive inborn error of metabolism leading to the accumulation of lipid in the abdominal organs. The condition is usually fatal by 6 months of age. On plain film, the adrenal glands are enlarged and densely calcified. Ultrasound demonstrates concomitant hepatosplenomegaly. CT confirms the adrenal origin of the calcifications. MRI demonstrates the adrenal high signal intensity on T1 sequences due to lipid deposition.[45,46]

As mentioned above, perinatal adrenal hemorrhage can subsequently calcify. Imaging characteristics can vary from a peripheral rim of calcification to complete replacement of the gland. Incomplete resolution of hematoma can result in a peripherally calcified rim around a nonenhancing pseudocyst.[46]

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CHAPTER 17

Adrenal Tumors and Functional Consequences

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INTRODUCTION

The pathogenesis, diagnosis, and management of adrenal tumors have recently evolved.[1,2] This is mainly because of the earlier discovery of insidious, clinically silent tumors. There are increasing numbers of incidentally detected adrenal tumors due to the use of more sensitive imaging procedures, such as computed tomography (CT) and magnetic resonance imaging (MRI).[3] Although these tumors are rare in children, it is important that the physician recognizes the clinical manifestations of these tumors as soon as possible, leading to earlier diagnosis, prompt intervention, and improved survival.

EPIDEMIOLOGY

Adrenal neoplasms are fortunately rare in the pediatric population, representing less than 1% of all solid tumors. Despite their infrequency, however, they can be fatal. Tumors arise from the medulla or cortex of the adrenal gland and can be benign or malignant. Malignant tumors account for 0.05%–0.2% of all malignancies in the pediatric population, with an incidence of less than 2 new cases per 1 million per year.[4,5] Adrenocortical carcinomas (ACCs) occur at all ages[6–11] and tend to present according to a bimodal distribution. The first peak occurs before the age of 5 years, and the second peak occurs in the fourth to fifth decade.[12] Females clearly predominate in all series, accounting for 65%–90% of the cases reported in the literature.[2] The reasons for this preponderance in women are unknown. Some authors have reported a left-sided prevalence; however, others state that bilateralism has been observed in 2%–10% of cases.[2,9] The incidence of ACCs is approximately 1 in 1.7 million in the general population.[13] They are seen in older patients compared with adenomas[14] and are more frequently encountered in females.[6] Moreover, they tend to be functional and may be part of hereditary syndromes. A retrospective review revealed that 92% of patients found to have a carcinoma presented with mixed endocrine syndromes versus 32% of patients with an adenoma,[15] the latter group presenting with only a virilizing syndrome.

MASSES OF THE ADRENAL CORTEX

Cortical tumors may be benign or malignant, functional or silent, all of which are rarely seen in children.[16–18] The identification and evaluation of these lesions can be very challenging, as it is often difficult to distinguish between the different types. Histopathology is the definitive confirmation; however, at times the clinical outcome may not even correlate with the histologic features.[19] Adrenal masses are often found incidentally and are nonfunctional in the general population, but in children, most are functional, leading to a more challenging diagnosis and treatment.

Associated endocrine syndromes resulting from secretion of cortisol and/or adrenal androgens and their precursors, or, rarely, estrogen or mineralocorticoids, may be seen in patients with functional neoplasms. They can produce syndromes of hypercortisolism and hyperaldosteronism, and rarely produce virilization or feminization. A more gradual onset of signs of hormone hypersecretion is generally observed in patients with adenomas, unlike those with ACC, who tend to have a more acute and progressive course.

Cushing's Syndrome

Hypercortisolism, or Cushing's syndrome, describes any form of glucocorticoid excess, which leads to protein catabolism, subsequent increased gluconeogenesis, and the typical symptoms associated with cortisol excess. Cushing's syndrome refers to patients presenting with a constellation of symptoms and signs regardless of the cause. It differs from Cushing's disease, which is caused by pituitary hypersecretion of the adrenocorticotropic hormone (ACTH). Cushing's syndrome in children is most commonly caused by an ACC and is seen in one-third to one-half of these patients.[20] One-fourth of the cases of endogenous Cushing's syndrome are caused by primary adrenal disease.

Aside from functional adrenocortical tumors and other usual causes, Cushing's syndrome can be particularly seen in children with primary pigmented nodular adrenocortical disease, which occurs as a component of Carney's complex. Also, infants found to have the McCune–Albright

syndrome can present with ACTH-independent Cushing's syndrome with nodular hyperplasia or adenoma formation. Finally, islet cell carcinoma of the pancreas, neuroblastoma or ganglioneuroblastoma, hemangiopericytoma, Wilms' tumor, thymic carcinoid, medullary thyroid cancer, and pulmonary neoplasms can lead to ectopic production of ACTH in the pediatric population.

Pathophysiology

ACTH is secreted in response to the corticotropin-releasing hormone (CRH) and vasopressin. It stimulates glucocorticoid cortisol secretion from the zona fasciculata and zona reticularis of the adrenal gland. The ensuing increased serum cortisol creates negative feedback on CRH, vasopressin, and subsequently ACTH. The amplitude and duration, but not the frequency, of ACTH secretory episodes are increased in Cushing's disease and the normal ACTH circadian rhythm is usually lost.[21] Cushing's syndrome occurs when there is a loss of the feedback mechanism of the hypothalamic–pituitary–adrenal axis, resulting in chronic exposure to excess circulating cortisol.

Constitutive activation of β-catenin has now been identified as a frequent alteration in benign and malignant adrenocortical tumors. The Wnt/β-catenin pathway is suggested to be essential in the development of the adrenal.[22] The ectopic constitutive activation could be associated with adrenal tumorigenesis considering the increased occurrence of adrenal tumors in patients with mutations of adenomatous polyposis coli (APC).[23] In a larger study including 100 surgically removed adrenal adenomas (excluding aldosteronomas), abnormal cytoplasmic and/or nuclear β-catenin immunohistochemical staining was found in about half; 36% had CTNNB1 mutations, mostly in larger and nonsecreting adenomas, suggesting that the Wnt/β-catenin pathway activation is associated with the development of less differentiated tumors.[24]

Clinical Findings

Signs and symptoms associated with hypercorticosolemia are variable. An important clinical manifestation is the simultaneous development and increasing severity of several of these symptoms. Typical symptoms and signs include moon facies, truncal obesity, and wide purplish striae. The most frequent and reliable findings in children with Cushing's syndrome are weight gain and growth failure,[25] and should highlight the possibility of the diagnosis.[6] Other findings may include hirsutism, muscle weakness, bruising, vertebral fractures, hypertension, and diabetes mellitus, but these are rarely seen. Lethargy, depression, acne, and menstrual irregularity[26,27] are other features observed. Patient's photographs may help in showing the clinical progression to a cushingoid state. In general, the clinical manifestation is more important in infants than in older children.

Laboratory Findings

Determining the presence of Cushing's syndrome is more important initially than identifying the cause.[28] Cushing's syndrome due to functioning adrenocortical tumors will exhibit elevated levels of several plasma and urinary steroids. These include cortisol following dexamethasone suppression test; dehydroepiandrosterone (DHEA) and its sulfate derivative (DHEAS); Δ^5-androstenediol, Δ^4-androstenedione, pregnenolone, 17-hydroxypregnenolone, and 11-deoxycortisol in the plasma; and free cortisol, 17-hydroxysteroids, 17-ketosteroids, and the tetrahydro metabolite of 11-deoxycortisol in the urine.[26] Measurements of other steroidogenic precursors, such as 17-hydroxyprogesterone and 11-deoxycortisol, may help if the presence of an adrenal malignancy in the patients with Cushing's syndrome is suspected.[27] Autonomous activity of the adrenal glands will lead to a low plasma ACTH level, associated with elevated plasma cortisol concentration.

Tumor Localization

Abdominal CT and/or MRI can document the existence of an adrenal lesion or bilateral nodular hyperplasia in cases of ACTH-dependent Cushing's syndrome. In patients with adrenal tumors, the contralateral adrenal should appear normal but could be atrophic since there is suppression of ACTH by the unilateral cortisol-secreting tumor.[29] It is often irresolute to determine between adenomas and carcinomas; however, tumors larger than 5 cm should be considered malignant until proven otherwise. Nevertheless, the diagnosis is ultimately confirmed by histopathology.[30,31]

Treatment

The treatment of Cushing's syndrome secondary to adrenal tumors is surgical. Unilateral adrenalectomy is performed for masses; however, bilateral adrenalectomy is completed for ACTH-dependent Cushing's syndrome not cured by other modalities. Measures to correct the hypercortisolemia and its metabolic sequelae are essential in preoperative preparation. Moreover, cortisol administration perioperatively should be given to prevent a state of hypoadrenalism. This is especially important in cases of total bilateral adrenalectomy, but also in cases of unilateral adrenalectomy, as the removal of the source of excessive cortisol in the presence of an invariably atrophied contralateral gland will inevitably lead to temporary or permanent adrenal insufficiency.

Medical treatment is indicated in patients who cannot undergo surgery or in those who have had unsuccessful resection of their tumor (pituitary, ectopic, or adrenal) with or without metastatic spread. Metyrapone, ketoconazole, aminogluthimide, mitotane, and etomidate have been used as inhibitors of steroid biosynthesis, and thus can be utilized in all cases of hypercortisolemia, regardless of cause, often with rapid improvement in the clinical features.

Prognosis

Surgical resection of an adenoma offers an excellent prognosis, whereas the outlook for patients with malignant tumors is poor. Children tend to have a better prognosis.[32,33]

Hereditary Syndromes

Although most cases of ACC appear to be sporadic, there are some that are associated with hereditary

cancer syndromes.[34] Multiple endocrine neoplasia type 1 (MEN 1) (parathyroid, pituitary, and pancreatic neuroendocrine tumors and adrenal adenomas or carcinomas) is connected to the inactivation of the MEN 1 gene on chromosome 11q. In addition, Beckwith–Wiedemann syndrome is associated with Wilms' tumor, neuroblastoma, and hepatoblastoma, and ACC is also linked with abnormalities in 11p15. Li–Fraumeni syndrome, which is related with inactivating mutations of the TP53 tumor suppressor gene on chromosome 17p, is associated with ACC in addition to breast cancer, soft tissue and bone sarcoma, and brain tumors. Finally, the SBLA syndrome, including sarcoma, breast and lung cancer, ACC, and other tumors, has not been localized to any chromosome.

Hyperaldosteronism

Aldosterone is the principal mineralocorticoid secreted by the adrenal gland. Increased secretion may be secondary to a primary defect (primary hyperaldosteronism) or result from factors that activate the renin–angiotensin system (secondary hyperaldosteronism).[94–96] Patients with primary hyperaldosteronism present with hypertention and/or hypokalemia; those with secondary hyperaldosteronism do not. Primary aldosteronism will lead to a state of mineralocorticoid excess with low plasma renin activity (PRA). It may be caused by the following pathologies: an aldosterone-producing adenoma (APA), idiopathic bilateral (BAH) or unilateral (UAH) adrenal hyperplasia, glucocorticoid-remediable aldosteronism (GRA), or rarely, an aldosterone-producing ACC. Adrenocortical hyperplasia is the most common cause in children.[8]

Although uncommon, unilateral APA has been described in children as young as 3.5 years and affects girls more frequently than boys. In 1954, Conn first reported that hypertension, hypokalemia, and metabolic alkalosis result from autonomous production of aldosterone by an adenoma. Since then, numerous studies have looked at the prevalence of primary aldosteronism and reported rates between 0.05% and 14.4% among hypertensive individuals.[35–38] BAH tends to occur in older children and affects males more frequently. Primary aldosteronism due to UAH has been reported infrequently in the pediatric population.[39–43] Adrenal carcinomas, an exceedingly rare cause of primary aldosteronism, are usually large (>5 cm) at the time of diagnosis.

Other states of mineralocorticoid excess with low PRA may include cases of congenital adrenal hyperplasia or Liddle's syndrome.[44] In these two syndromes, non-aldosterone-mediated renal sodium reabsorption results in volume expansion and suppression of both PRA and plasma aldosterone (PA).

At the other end of the spectrum, other patients may present with a state of mineralocorticoid excess with high PRA. They may be hypertensive (renovascular disorders, coarctation of the aorta, or renin-secreting tumors) or normo- or hypotensive with reduced circulating blood volume (Gitelman's syndrome, Bartter syndrome, pseudohypoaldosteronism type 1, or diuretic use), or have a reduced "effective" circulating blood volume (congestive heart failure, hepatic cirrhosis, or nephrotic syndrome).

Physiology of Aldosterone

Aldosterone synthesis is orchestrated by the renin–angiotensin system. Renin, produced in the juxtaglomerular apparatus, catalyzes the conversion of the angiotensinogen to angiotensin I. Angiotensin I undergoes further enzymatic conversion by angiotensin-converting enzyme (ACE) to produce angiotensin II, which acts to stimulate the production of aldosterone from the zona glomerulosa. The renin–angiotensin II system is also expressed locally and regulates aldosterone production in a paracrine fashion. Aldosterone's release is positively and directly modified by potassium balance. It can also be modulated by other factors, such as ACTH, dopamine, and atrial natriuretic peptide.

Clinical Findings

Signs and symptoms of hyperaldosteronism are nonspecific, often resulting in or associated with hypertension with headache, dizziness, and visual disturbances. However, some individuals have minimal elevation of blood pressure. Therefore, hypertension is not a sine qua non for this disorder.[12] In reality, the most common finding remains hypokalemia. Chronic hypokalemia may lead to "clear cell nephrosis," polyuria, nocturia, enuresis, and polydipsia. Muscle weakness and discomfort, tetany, intermittent paralysis, fatigue, and growth failure may also be observed in these children. Classic features of moderate to severe hypertension, hypokalemia, and metabolic alkalosis are highly suggestive of mineralocorticoid excess. However, only subtle clues of hyperaldosteronism exist in the majority of cases, such as the recent onset of refractory hypertension.

Laboratory Findings

Hyperaldosteronism can generally be proven by measurements of aldosterone and PRA, 11-deoxycorticosterone, and/or corticosterone, respectively. Plasma and urine levels of aldosterone are increased, and plasma levels of renin are persistently low.[35–37] In addition, the serum pH, carbon dioxide content, and sodium concentrations may be increased, and the serum chloride and magnesium levels can be decreased. Serum levels of calcium are normal, even in children who manifest tetany. The urine is neutral or alkaline, and kaliuresis is present. Aldosterone does not decrease with sodium chloride administration, and renin does not respond to salt and fluid restriction.

Differential Diagnosis and Tumor Localization

All cases with a history of hypertension associated with "spontaneous" or severe hypokalemia precipitated by diuretic therapy should suggest the diagnosis of primary aldosteronism. Suspicion is also warranted in all incidentally discovered adrenal masses, especially in a hypertensive individual.[45] Once the diagnosis is established, it is necessary to identify the underlying cause (APA, BAH, UAH, GRA, or an aldosterone-producing ACC).

All children should have a therapeutic trial with daily administration of dexamethasone before invasive studies are carried out, since this test is easy to perform. A marked

suppression of aldosterone and disappearance of hypertension is observed in patients with the glucocorticoid-suppressible variant of hyperaldosteronism or GRA.

If there is no response, CT scanning or MRI may reveal a mass within the adrenal. In cases of inconclusive data or equivocal radiographic features, however, adrenal vein sampling of aldosterone and cortisol is recommended to differentiate between an adenoma and hyperplasia.[46–49]

Treatment

GRA is managed by daily administration of glucocorticoid. The treatment of a functional adenoma is excision. Resection is frequently curative or improves hypertension and invariably treats the hypokalemia. In one recent analysis, however, only one-third of patients became normotensive postoperatively.[50] In patients known to have an APA, suppression of aldosterone secretion in the contralateral adrenal gland is expected, thus resulting in a transient hyporeninemic hypoaldosterone state.[51] Therefore, sodium restriction could increase the risk of dehydration. Pharmacologic treatment of BAH with spironolactone or amiloride usually results in normalization of the blood pressure and serum potassium levels. Management of secondary hyperaldosteronism is directed toward the specific causative agent.

Virilizing Tumors

Abnormal virilization is seen in cases of ACC in two-thirds of the adult patients,[52] whereas it is the most common hormonal syndrome in children with adrenocortical tumors.[2,8,10,53] Virilization is due to hypersecretion of adrenal androgens, including DHEA and DHEAS, Δ^5-androstenediol, and Δ^4-androstenedione, all of which may be converted to testosterone and 5α-dihydrotestosterone.

In adult females, the signs and symptoms include oligoamenorrhea, hirsutism, acne, excessive muscle mass, temporal balding, increased libido, and clitoromegaly. In young girls, precocious puberty occurs. Cushing's syndrome, combined with signs of virilization, is seen in 10%–30% of all patients.[2,3,54]

Measurement of plasma adrenal androgens, testosterone, and 24 h urinary excretion of 17-ketosteroids may confirm the clinical diagnosis of adrenally induced virilization.

Androgen-secreting adrenal tumors are usually malignant, but benign tumors have also been described in women. In a series of 21 women with androgen-secreting tumors, malignant tumors ($n = 10$) were larger at presentation than benign tumors ($n = 11$; 14 vs. 9 cm, respectively). Moreover, in women with malignant tumors, serum testosterone levels were 2.6-fold higher.[55] In benign cortisol-secreting adenomas, serum androgen levels are usually not high but can produce small amounts of androgen.[56]

Feminizing Adrenal Tumors

Estrogen-secreting tumors are rare and are usually malignant.[57] In males, they can present as feminization with gynecomastia, decreased libido, and testicular atrophy; in women, they can present with breast tenderness and dysfunctional uterine bleeding. They can be confirmed by measurements of elevated plasma estradiol and/or estrone.[58]

MASSES OF THE ADRENAL MEDULLA

Pheochromocytoma

Pheochromocytomas are rare neoplasms in children. They are neuroendocrine tumors that arise from neural crest–derived chromaffin cells in the adrenal medulla. During embryologic development, chromaffin cells migrate to the adrenal medulla. Pheochromocytomas are catecholamine-secreting tumors. Ninety percent arise from the medullary portion of the adrenals, whereas 10% occur in extra-adrenal chromaffin tissues (paragangliomas). About 10% are familial, multicentric, and bilateral, whereas the remainder are sporadic. The incidence in the hypertensive population varies between 0.05% and 0.1%.[99]

Pheochromocytomas are uncommonly observed in children, and the true incidence is unknown. Indeed, it appears that this tumor of neuroectodermal origin is more common in adults. Most of what is known on the behavior and management of these tumors arises from the adult literature. In children, the age of presentation is around 10 years; there is a male propensity in most series, an increased incidence of bilaterality (20%) and multifocality, a lower incidence of malignancy (2.4%–3.5%), and a greater tendency for familial occurrence.[59]

Familial pheochromocytomas can occur with or without an association to known familial cancer syndromes (MEN 2, von Hippel–Lindau disease, neurofibromatosis type 1, Sturge–Weber syndrome, and familial carotid body tumors).[60] It appears that hereditary forms can evolve differently in terms of tumor growth rate and malignancy potential. Thus, individuals with familial pheochromocytomas are diagnosed at a younger age and tend to have bilateral or multifocal lesions that are usually benign.

Signs and Symptoms

Signs and symptoms are related to excessive tumor secretion of catecholamines produced in large amounts by pheochromocytes. Hypertension is the most common sign, and in children, it is more sustained than paroxysmal symptoms. Other signs and symptoms could include postural hypotension, headaches, increased sweating, pallor, flushing, tachycardia, weight loss, constipation, weakness, and visual anomalies. The symptoms most frequently observed in children include headaches, nausea, vomiting, constipation, weight loss, and visual complaints.[61,62] A palpable mass and sustained hypertension are strongly suggestive of the diagnosis. However, a palpable mass may be the sole finding.

Diagnosis

The biochemical diagnosis is made from the measurements of catecholamines and catecholamine metabolites in plasma or urine.[63–67] Norepinephrine and epinephrine are produced by the sympathoneuronal and sympathomedullary

systems, and therefore are not specific to pheochromocytomas. Other limitations relate to the fact that increased plasma catecholamine levels may be produced by a variety of conditions (e.g., emotional stress, physical activity, eating, and fever). Some pheochromocytomas may not secrete catecholamines at all or may secrete them episodically. Glucagon stimulation and clonidine suppression tests are useful in some patients to further confirm the diagnosis of pheochromocytoma.[61,68,69]

Tumor Localization

Pheochromocytomas can be imaged with CT, MRI, and/or scintigraphy after administration of ^{131}I- or ^{123}I-labeled metaiodobenzylguanidine (MIBG).[70–73] If an initial abdominal CT or MRI is positive, whole-body MIBG should be performed to confirm the diagnosis. If abdominal studies are negative, then the whole-body evaluation by CT or MRI is indicated. If an initial MIBG scan is positive, then CT or MRI follows to more precisely localize a mass. However, a negative MIBG scan does not exclude a pheochromocytoma. More recently, positron emission tomography (PET) has been used in particular cases.

Treatment

The definitive treatment of pheochromocytoma is surgical excision of the tumor. Of particular interest, patients with pheochromocytomas should undergo pharmacologic blockade (α and β) of catecholamine effects and synthesis prior to surgery, as well as aggressive correction of the hypovolemia perioperatively to avoid hypotension. Intraadrenal pheochromocytomas can be removed successfully by laparoscopy, which minimizes catecholamine-induced hemodynamic changes during operation.[74]

Neuroblastic Tumors

Neuroblastic tumors will be briefly reviewed in this chapter. Neuroblastic tumors include ganglioneuroma, ganglioneuroblastoma, and neuroblastoma, which are tumors of the sympathetic nervous system.[75] They arise wherever sympathetic tissue exists and are found in the neck, posterior mediastinum, adrenal gland, retroperitoneum, and pelvis. The adrenal gland is the most common site.[100,118]

The most benign tumor is the ganglioneuroma, which is composed of gangliocytes and mature stroma.[76,77] It arises from the medulla in less than half of the cases found to have an abdominal ganglioneuroma.[78–81] Patients of all ages are affected, predominantly children and young adults (42%–60% of cases),[75–85] and they are often asymptomatic. Otherwise, abdominal pain or abdominal mass is the most common finding.[74] Hormonally active tumors have been reported, and the secretion of catecholamines, vasoactive intestinal polypeptides, or androgenic hormones explains such symptoms as hypertension, diarrhea, and virilization.[82–84,86–88] The prognosis is excellent, and recurrence is rare after surgical removal.[83,89]

Ganglioneuroblastomas are transitional tumors of sympathetic cell origin that contain elements of both malignant neuroblastoma and benign ganglioneuroma. The most common tumor location is the abdomen. This tumor is most often seen in patients who are 2–4 years old and is rarely seen after 10 years.[90] The prognosis and response to therapy are significantly more favorable than with neuroblastomas.[91]

Neuroblastoma is the most immature, undifferentiated, and malignant tumor of the three that consist of primitive neuroblasts.[92] Neuroblastomas, which account for 97% of all neuroblastic tumors, are heterogeneous, varying in terms of location, histopathologic appearance, and biologic characteristics.[93] They are most remarkable for their broad spectrum of clinical behavior, which can range from spontaneous regression to aggressive disease with metastatic dissemination leading to death.[94,101–112,119]

METASTATIC LESIONS

Metastatic lesions to the adrenal gland are uncommon, but when present, they tend to have an irregular shape and are inhomogeneous in nature. They have a tendency to be bilateral and have high unenhanced CT attenuation values, enhancement with intravenous contrast, and delay in contrast washout. They can include leiomyosarcomas, lymphoma, malignant melanoma, squamous cell carcinoma of the lung, hepatocellular carcinoma, and breast cancer.[97,98,112,115]

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CHAPTER
18

Surgery of the Adrenal in Pediatric Patients

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INTRODUCTION

Adrenal surgery has an extensive and constantly evolving history, beginning with the first description of an adrenalectomy in 1914 by British surgeon Perry Sargent.[1] Since that time, understanding of the physiology and pathophysiology of the adrenal gland has become better understood, while advances in imaging of the adrenal gland have improved disease localization. The surgical approaches have also evolved with the advent of and improvements in minimally invasive surgery (MIS). The spectrum of pediatric adrenal disease and the pathophysiology governing these processes have been covered in previous chapters. The focus of this chapter is on the surgical management of adrenal disease, with special consideration for the development of minimally invasive techniques in pediatrics.

MINIMALLY INVASIVE ADRENALECTOMY

Endoscopic surgery in pediatric patients dates back to 1971, when Gans and Berci[2] investigated and reported on a case series of minimally invasive procedures on infants and children. Since then, the types and quantity of MISs have increased, with significant advancements in technology and proficiency. Laparoscopic adrenalectomy was first described by Gagner et al. in 1992,[3] and since then has rapidly replaced open adrenalectomy (OA) as the criterion standard for adrenal surgery in adults.[4–9] Multiple large studies have found that minimally invasive adrenalectomy (MIA) is associated with decreased length of hospital stay, decreased operative times, decreased reoperation rates, decreased postoperative complications, and decreased morbidity rates even after adjustment for confounding factors.[4,5,10]

However, these results should not necessarily be applied to the pediatric population because of significant differences in patient characteristics, including comorbidities and patient size, and in the rates of benign versus malignant tumors. Neuroblastoma, which represents the most common adrenal tumor in children, is characterized by an infiltrative growth pattern that was originally seen as a contraindication to MIA. However, continued experience with laparoscopy and robot-assisted surgery, along with continued improvements in surgical instrumentation, has expanded the indications for and use of MIA in pediatric adrenal surgery.

The largest pediatric studies involving MIA demonstrate a low morbidity rate ranging from 0% to 10% for well-encapsulated masses without image-defined risk factors (IDRFs).[11–15] Port site recurrence of cancerous tumors has not been described in any children after MIA.[16] Children undergoing MIA have a significantly shorter length of stay than those undergoing OA.[17] MIA may also provide several potential advantages over OA, including decreased rates of intestinal obstruction, decreased levels of postoperative pain, and improved cosmetic results. The rates of postoperative intestinal obstruction are significantly lower after MISs (0.9%)[18] than after open abdominal tumor surgeries (3.7%).[18,19] Although improved postoperative pain control has been assumed to be an advantage of MIS in comparison with open procedures in pediatric populations, several randomized controlled trials found no significant differences in pain control.[20–22] However, these trials were for short procedures with small parietal incisions (e.g., appendectomy, pyloromyotomy, and pyeloplasty). OA is performed with a large transperitoneal incision compared with the subcentimeter incisions with MIA, which could potentially lead to significantly decreased postoperative pain levels. In addition, long-term cosmetic results can have a significant impact on the quality of life in children who survive a malignant tumor. MIA has a significant advantage in this regard, with 5 or 10 mm incisions compared with the large transperitoneal incisions utilized for OA.

APPROACHES TO MINIMALLY INVASIVE ADRENALECTOMY

MIA can have significant advantages over OA in children for well-encapsulated masses without IDRFs. MIA can be performed using multiple approaches, including the transperitoneal adrenalectomy (TA) and prone retroperitoneal (PRA), and lateral retroperitoneal (LRA) approaches, as well as robot-assisted adrenalectomy (RAA) and single-port techniques. We will discuss each of these approaches, and comment on their advantages.

Laparoscopic Transperitoneal Adrenalectomy

Patients are placed on a clear liquid diet the day prior to surgery and given a mechanical bowel preparation. After the patient is intubated, a Foley catheter is inserted into

the bladder, and the stomach is decompressed with an oral gastric tube. We place the patient in a semilateral decubitus position, with the side of the lesion elevated approximately 45°, and flex the operating table. The patient is draped from the nipple line to the lower abdomen and across the midline, allowing for possible open conversion. The patient is rolled to a near-supine position, and pneumoperitoneum is established. We prefer the Hasson open, cut-down technique for establishing the pneumoperitoneum in the pediatric population. The first trocar, an 11–12 mm trocar, is placed in the midline just above the umbilicus. The peritoneal space is insufflated to 12–15 mmHg using CO_2, and the abdominal cavity is explored with a 10 mm, 30° laparoscope. The table is then rolled to a full flank position for additional trocar placement.

For left TA, two accessory trocars are inserted: a 5 mm port 3–4 cm cephalad to the supraumbilical trocar, and a 5 mm port in the midclavicular line, below the costal margin (Figure 18.1). Port placement may vary slightly with the age and size of the child. Adhesions of the left upper quadrant to the anterior abdominal wall are first identified and incised using the harmonic scalpel. The splenic flexure of the left colon is then mobilized by incising the peritoneum along the line of Toldt. The spleen is mobilized by incising its attachments to Gerota's fascia, the abdominal side wall, and the diaphragm with the harmonic scalpel or electrocautery shears. Dissection of the lateral splenic attachments is carried out until the gastric fundus is visualized. At the conclusion of this dissection, the spleen should fall medially without the need for retraction.

Once the splenic flexure and spleen are mobilized, the plane between the tail of the pancreas and Gerota's fascia is developed to release the pancreas medially. The superior border of the adrenal gland is then dissected from lateral to medial. The inferior phrenic vessels are identified, clipped, and divided as they are encountered along the upper aspect of the adrenal. The lateral-most attachments of the gland are left intact to hold the gland in place and thereby facilitate the remainder of the dissection. Dissection is continued medially along the gland, where the arterial supply to the adrenal from the aorta is encountered, clipped, and divided. Inferiorly, the left adrenal vein is identified entering the left renal vein, clipped, and divided.

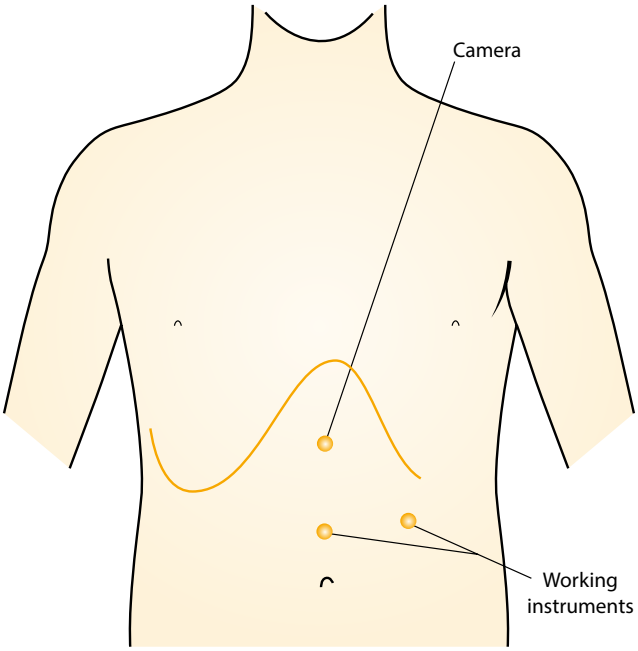

FIGURE 18.1 Port placement for transperitoneal laparoscopic left adrenalectomy. The supraumbilical working instrument is 11–12 mm, to facilitate insertion of a clip applier.

Division of the left adrenal vein often reveals an inferior adrenal artery arising from the left renal artery; if encountered, this artery should be clipped and divided. Finally, the lateral attachments of the adrenal are divided, releasing the gland. The adrenal is placed in a retrieval bag inserted through the umbilical port. Visualization for the remainder of the procedure is accomplished with a 5 mm, 30° scope placed through the port in the midclavicular line. The bag containing the specimen is temporarily placed on the kidney, and the operative bed irrigated and inspected for bleeding. Once hemostasis is ensured, the specimen is then removed from the patient; the trocar site may be enlarged if necessary to facilitate the removal of larger glands. The remaining ports are then removed and closed.

Laparoscopic right TA is performed using three accessory trocars, because of the need to retract the liver. After insufflations, a 5 mm port is placed 3–4 cm cephalad to the supraumbilical trocar (as for the left adrenalectomy), while two 5 mm ports are placed laterally below the costal margin in the anterior axillary and midclavicular lines. After adhesions of the right upper quadrant to the anterior abdominal wall are incised, the liver is mobilized from the abdominal side wall and diaphragm by incising the triangular and coronary ligaments. The extent of mobilization of the liver necessary for exposure increases with age in children, as the distance between structures increases and the flexibility of tissues decreases. A liver retractor is then introduced through the anterior axillary line trocar to reflect the liver away from the adrenal (Figure 18.2). With the liver mobilized, the anterior wall of the vena cava is identified, and the medial attachments of the adrenal gland are released. The duodenum is mobilized medially, exposing the renal hilum. As the dissection is carried cephalad on the anterior wall of the cava, the right adrenal vein is identified. We secure the vein by doubly clipping both the patient and specimen sides of the vein and then sharply dividing the vein between the clips (Figure 18.3). Once the adrenal vein has been controlled, the superior and inferior aspects of the adrenal are sequentially dissected as for a left adrenalectomy, dividing the inferior vascularized pedicle, which arises from the right renal hilum, on the caudal border of the gland. The adrenal gland is then mobilized off the upper pole of the kidney by incising Gerota's fascia at the junction of the upper pole and adrenal using the harmonic scalpel. The lateral attachments, left intact to maintain the gland in position for dissection, are released last, and the adrenal removed.

Postoperatively, patients are started on clear liquids on the night of surgery, and their diet is advanced as tolerated. The Foley catheter is removed on the first postoperative day, and patients are typically discharged after passing a trial of voiding.

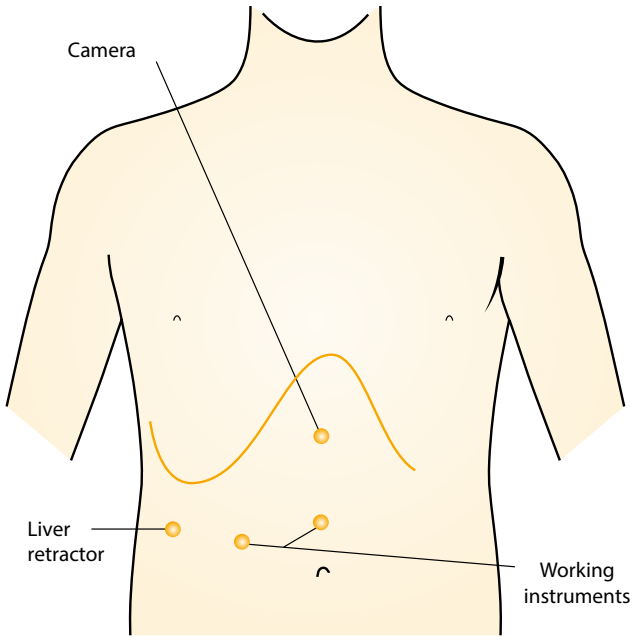

FIGURE 18.2 Port placement for transperitoneal laparoscopic right adrenalectomy. Note the additional trocar in the anterior axillary line for liver retractor.

Prone Retroperitoneal Adrenalectomy

The patient is placed in a fully prone position, with attention paid to place the patient close to the border of the operative table on the side of the operation in order to provide full range of motion of the lateral port. The thorax and pelvis are elevated to free the abdomen. The initial incision is made halfway between the iliac crest and the 12th rib at the lateral border of the vertebral muscles.

The retroperitoneal space outside Gerota's fascia is dissected out. The working space in the retroperitoneum is established using balloon distention. We prefer fashioning a balloon for distention by securing the finger of a surgeon's glove to a 16 Fr red rubber catheter. Once the balloon is introduced into the retroperitoneal space, the glove tip is filled with 100–500 cc of saline and left inflated for 5 minutes to develop the retroperitoneal space. The balloon is then removed and a 10 mm Hasson trocar is introduced into the space and pneumoretroperitoneum established to a pressure of 12 mmHg. Two additional ports are then placed, a 3 mm port at the tip of the 12th rib and a third 5 mm port between the two prior ports.

The same landmarks are used for dissection as in TA, with care to identify the inferior vena cava (IVC) on the right side, and the splenic and renal veins on the left. The specimen is then delivered through the medial incision.

Retroperitoneal laparoscopy has been well described for a variety of procedures in adults since the initial description by Gaur.[23] The potential advantages of the retroperitoneal approach include more direct access to the adrenal glands, easier identification of the vascular landmarks, decreased risk of injury to the intra-abdominal organs, safety in patients who had prior abdominal trauma or surgery, and the possibility of bilateral procedures in one surgical position. However, there are significant disadvantages that must be taken into account. There is a more limited working space, which is a particular challenge in the pediatric patient population.[24] In addition, pediatric surgeons are much less familiar with this approach. The largest adult study of PRA in 520 patients by Walz et al.[25] found that there is a significant learning curve in PRA, and that there was a continuous decrease in operative time as the surgical experience increased.

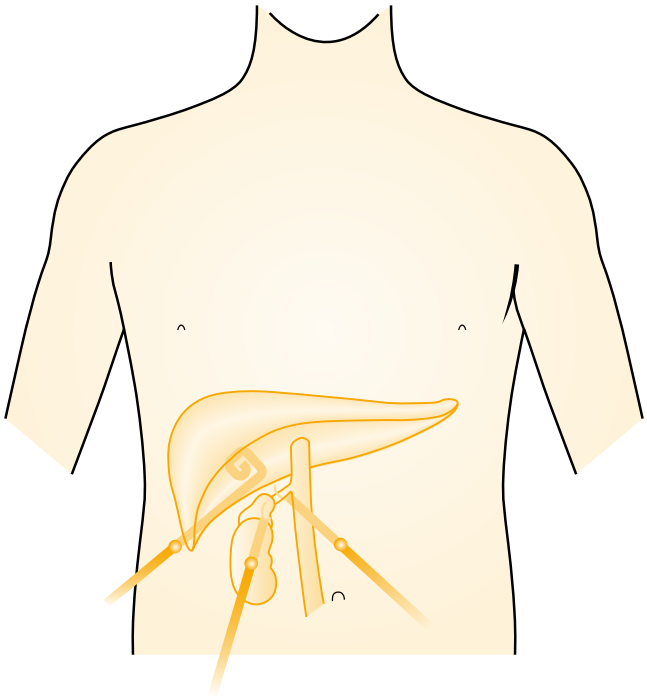

FIGURE 18.3 Transperitoneal laparoscopic exposure and ligation of the right adrenal vein.

Lateral Retroperitoneal Adrenalectomy

We position the patient in a flank position, and gain initial access through an incision below the tip of the 12th rib, just superior to the anterior iliac spine. Dissection is carried out bluntly through the external and internal oblique muscles and the transversus abdominus muscle into the retroperitoneum. The peritoneum is swept medially, and a working space in the retroperitoneum is established using balloon distention. The retroperitoneum working space is opened in a fashion similar to that of the PRA approach, with a modified homemade balloon. A 10 mm Hasson trocar is introduced into the space, and the pneumoretroperitoneum established to a pressure of 12 mmHg. Two additional 5 mm trocars are placed in the posterior and anterior axillary lines, superior to the Hasson trocar. For right adrenalectomy, the vena cava is identified medial to the psoas muscle, and dissection is carried superiorly along the vena cava to identify first the renal hilum and then the right adrenal vein, which is ligated using hemoclips. The medial and inferior margins of the adrenal are dissected, dividing the adrenal arteries with the harmonic scalpel or clips as they are encountered. The superior aspect of the gland is mobilized as well, and the adrenal is then

dissected free from the upper pole of the kidney. As with the TA, the lateral attachments of the gland are released last, and the adrenal is removed.

The initial dissection for a left LRA identifies the renal hilum. The left renal artery is retracted inferiorly, revealing the adrenal vein as it enters the left renal vein. The adrenal vein is ligated with hemoclips and divided. The adrenal gland is then dissected along its perimeter, using the harmonic scalpel and hemoclips as needed. For a left-sided LRA, the medial attachments of the gland are left intact to facilitate dissection, while the superior, lateral, and inferior mobilization of the adrenal is completed. The medial attachments are released last, and the specimen is removed.

Robot-Assisted Adrenalectomy

The first RAA was reported by Piazza et al.[26] in 1999 using the Zeus AESOP system. Since then, major improvements in the technology and increasing familiarity with minimally invasive techniques have allowed for broader applications of robot-assisted procedures. The first RAA was described by Horgan and Vanuno[27] using the da Vinci® Surgical System (Intuitive Surgical, Sunnyvale, California). Robot-assisted surgery provides the surgeon with magnified three-dimensional vision, seven degrees of freedom, scaling of movement, and minimization of tremor, which make this technology ideal for pediatric patients.

Multiple case series have found that RAA can be performed safely with lengths of stay and complication rates comparable to those of open and other laparoscopic procedures.[28–33] In one of the largest series of 100 consecutive adult patients, Brunaud et al.[33] found that RAA could be safely performed with low complication rates. For technically difficult masses, such as large adrenal masses greater than 5 cm, RAA may provide a benefit compared with laparoscopic techniques; Agcaoglu et al.[29] found that those undergoing RAA had significantly shorter operative times, shorter hospital stays, decreased open conversion rates, and lower complication rates. Conversely, Morino et al.[34] performed a small, randomized controlled trial comparing RAA with laparoscopic adrenalectomy that showed a higher open conversion rate for RAA. A meta-analysis by Brandao et al.[35] concluded that operative time and open conversion rates are similar between RAA and laparoscopic adrenalectomy, while blood loss and hospital stay were improved for RAA. As there have been no well-powered randomized controlled trials comparing RAA with laparoscopic adrenalectomy or OA in the adult or pediatric population, a direct comparison of outcomes among series is potentially biased. Future studies will be needed to clearly define the role of robotic surgery, especially in pediatrics.

The costs involved with the instrumentation are more expensive for the robotic procedure than for traditional laparoscopy.[33] However, with significantly shorter hospital stays and decreased pain requirements, the overall hospital costs of RAA are similar to, if not significantly less than, traditional laparoscopy. In addition, when accounting for the human capital calculations, especially regarding loss of parental workdays and loss of potential wages, robot-assisted surgeries could have significant advantages over other techniques.[36]

RAA can be performed through any of the previously mentioned laparoscopic approaches, the PRA, transabdominal adrenalectomy, or LRA. In the retroperitoneal approach, the patient is placed in a jackknife position with the use of a Wilson frame. A transcutaneous ultrasound can be used to map out the location of the ipsilateral kidney, 12th rib, and adrenal gland. An incision is made 2 cm inferior and parallel to the 12th rib. An optical trocar can then be placed to enter Gerota's space, and the working space can be defined by a 10 mm dissecting balloon under direct vision. This trocar can then be replaced by a 12 mm long trocar, with insufflations kept between 15 and 20 mmHg. Two 5 mm trocars are then inserted on either side of the trocar, taking care to optimize the distance between the trocar and camera port to avoid port site conflicts. The operating table is then rotated 30° clockwise, and the robot is brought in from the head of the table. A robotic grasper is then placed in the medial port and a robotic harmonic scalpel in the lateral port. The dissection can then continue from the superolateral border to the inferior border, and finally to the medial border. The adrenal vein is then identified and divided between two 5 mm clips placed by an assistant.

In the transperitoneal approach, the patient is placed in a semilateral decubitus position with either a bean bag or roll. We prefer the Hasson open, cut-down technique for establishing the pneumoperitoneum in the pediatric population; however, other techniques, such as the Veress needle, can also be used. A 10 mm trocar is placed in the midline just above the umbilicus. The peritoneal space is insufflated to 12–15 mmHg using CO_2. Two 5 mm robotic ports can then be placed, one port 1 cm inferior to the costal margin in line with the optical port, and another 3 cm inferior to the optical port in the midclavicular line. One additional 5 mm port can be inserted for bedside laparoscopic assistance.

Single-Port Techniques

Laparoscopic single-port surgery, called laparoendoscopic single-site (LESS) surgery, single-port access (SPA), or single-incision laparoscopic surgery (SILS), depending on the manufacturer, has been increasingly used as comfort and experience with laparoscopy continues to improve and the instruments continue to improve. Compared with robot-assisted procedures or laparoscopic procedures that utilize multiple incisions that are significant in size in relation to the patient size, single-port surgery may be advantageous in children. Initially used for appendectomies and cholecystectomies, more centers are starting to develop single-port techniques for adrenalectomy.[37–43] The single-port technique can be used for TA, PRA, or LRA and usually involves a single scope and two ports through a single access sheath in one incision. A case control study by Walz et al.[42] of a single-port retroperitoneal adrenalectomy versus a conventional retroperitoneal adrenalectomy found that the single-port technique had significantly shorter hospital stays with no differences in complication rates, but had higher open conversion rates and longer operative times.

OPEN ADRENALECTOMY

MIA in the pediatric population is continuously evolving. However, given the relative inexperience with MIA in children and the predominance of neuroblastomas, which may not be amenable to MIA, pediatric surgeons and urologists should be familiar with the various open approaches to adrenalectomy as well.

Flank Approach

The standard extrapleural, extraperitoneal flank approach to the adrenal gland may be performed for either left or right adrenalectomy. This technique offers the advantage of utilizing the positioning and initial exposure, similar to radical nephrectomies (Figure 18.4). For right adrenalectomy, the retroperitoneal space is first identified by medial reflection of the colon and duodenum. The liver is dissected off the anterior surface of the adrenal, allowing ligation of the superior vasculature to the gland. This dissection is facilitated by inferior traction on the kidney, and the mobilization is continued along the posterior abdominal wall and diaphragm from lateral to medial. The small arterial branches to the adrenal should be divided with hemoclips as they are encountered. The IVC is then exposed, and the adrenal vein identified, dissected free, and divided with clips or ties. The inferior attachments of the adrenal to the kidney are released last, allowing removal of the gland.

Mobilization for left adrenalectomy begins with division of the splenorenal ligament. Gerota's fascia can be swept medially, and the pancreas retracted superiorly and medially, exposing the adrenal. The superior attachments of the adrenal are released from lateral to medial, leading to the renal hilum. The adrenal vein is isolated at its entry to the renal vein, where it is divided. The inferior aspect of the gland is dissected off the upper pole of the left kidney, and the gland is then removed.

Thoracoabdominal Adrenalectomy

The main indication for a thoracoabdominal approach to the adrenal gland is to provide maximum exposure for large tumors, particularly on the right side, where the liver and vena cava can impede exposure. However, this technique may increase pulmonary complications, as the diaphragm is divided and the thoracic cavity entered.[44] The patient is positioned in approximately 45° flank, and the incision is made through either the eighth or ninth intercostal space (Figure 18.5). The intercostal muscles are encountered and divided, revealing the muscle fibers of the diaphragm, which are circumferentially divided. Adrenalectomy is then performed as described above for the flank approach. At the conclusion of the procedure, a thoracostomy tube is placed in the ipsilateral hemithorax, and the diaphragm is closed using interrupted silk sutures.

Posterior Adrenalectomy

Currently, we use the open posterior approach to adrenalectomy primarily for simultaneous bilateral adrenalectomy, as in patients with Cushing's disease.[44] Patients are placed in the prone position, and an oblique incision is made overlying the 11th or 12th rib (Figure 18.6). After subperiosteal rib resection, the diaphragm and pleura are mobilized superiorly to expose the retroperitoneal space. For left adrenalectomy, the splenorenal ligament is first released laterally, and dissection then proceeds along the superior aspect of the gland from

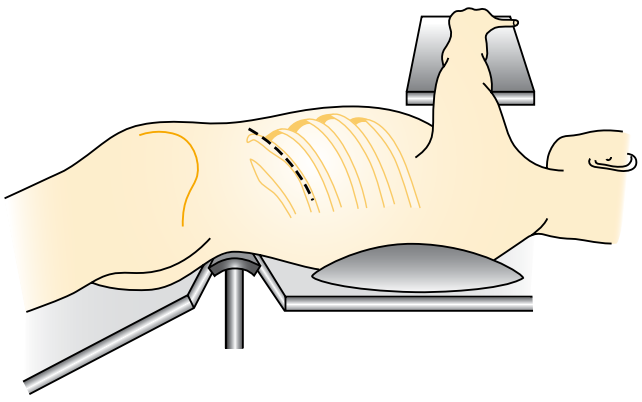

FIGURE 18.4 Positioning for flank approach to left adrenalectomy. The dotted line marks the 11th rib incision.

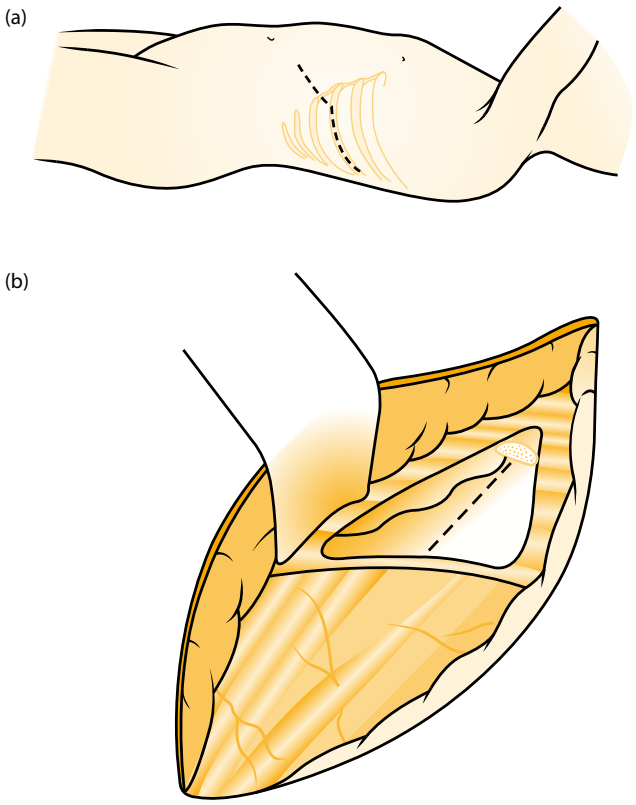

FIGURE 18.5 (a) Incision overlying the ninth rib for thoracoabdominal left adrenalectomy. (b) Exposure after resection of rib (seen cut at top of figure). The dotted line marks the incision in the diaphragm muscle.

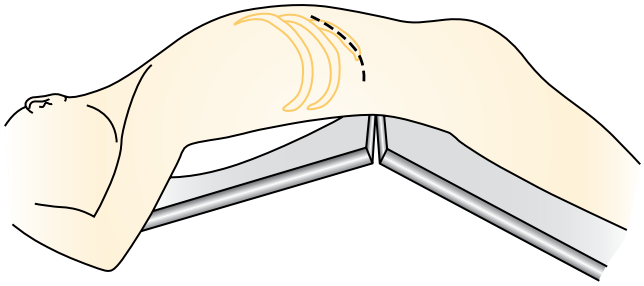

FIGURE 18.6 Positioning for (standard) posterior approach to adrenalectomy.

lateral to medial. This dissection may be facilitated by downward manual traction on the kidney. Medially, the left adrenal vein is identified and divided with clips or ties at its insertion into the left renal vein. Dissection is completed along the inferior aspect of the gland, and the adrenal is removed.

For a posterior right adrenalectomy, the liver is initially dissected off the adrenal and retracted cephalad. The superior vascular attachments of the gland are then divided from lateral to medial, until the vena cava is exposed. The lateral wall of the vena cava is dissected to the origin of the right adrenal vein, which can be clipped or tied and divided. After division of the vein, the inferior attachments of the gland are released, and the adrenal is removed. Given the often difficult exposure of the right adrenal vein through this (standard) posterior approach, we perform open right adrenalectomy via a modified posterior approach, where the patient's position on the operating table approximates that used during a Gil-Vernet dorsal lumbotomy incision (Figure 18.7).[45] An 11th or 12th rib incision is made, and the liver is mobilized as described above. However, as the vena cava is exposed by division of the superior attachments of the gland, the adrenal vein is encountered coursing toward the operating surgeon, thereby facilitating its identification and division. In the (standard) posterior approach, the vein lies in a posterior position and is thus at risk of avulsion during exposure.[46] The remainder of the dissection proceeds as for the standard posterior approach.

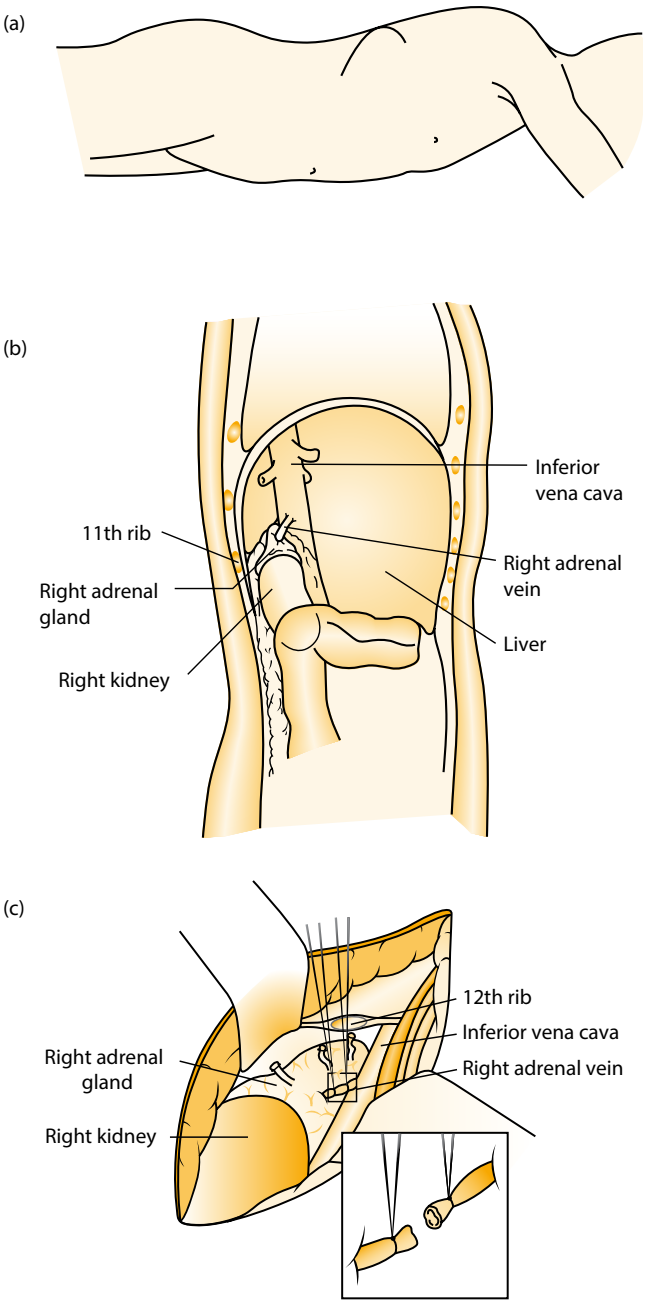

FIGURE 18.7 Modified posterior right adrenalectomy. (a) Positioning and incision. (b) View of adrenal bed, with right adrenal vein visible, seen during this approach. (c) Exposure and division of right adrenal vein.

Transabdominal Adrenalectomy

Transabdominal adrenalectomy is indicated primarily to facilitate complete abdominal exploration, as in the case of multiple pheochromocytomas, for patients with large adrenal carcinomas, and for adrenal lesions with involvement of the IVC. A chevron incision is used to gain access to the peritoneum, which is then systematically explored for lesions and metastases. Once this has been accomplished, right adrenalectomy may be performed by reflection of the hepatic flexure of the colon inferiorly and incision in the posterior peritoneum lateral to the kidney. This allows reflection of the liver superiorly and exposes the anterior vena cava, approximately at the level of the renal hilum. Cephalad dissection along the anterolateral wall of the vena cava leads to the right adrenal vein, which is then divided. The superior vasculature of the adrenal is released next, proceeding from the medial to the lateral aspects and facilitated by downward manual traction on the kidney. Lastly, the inferior attachments of the adrenal to the right kidney are mobilized.

For left adrenalectomy, the colon is first reflected medially, and the renal hilum identified and dissected. The left adrenal vein is divided as it enters the left renal vein. The anterior adrenal surface is then exposed by mobilization of the pancreas and spleen. The remainder of the dissection proceeds from the medial to the lateral aspect along the superior and inferior borders of the gland.

COMPLICATIONS OF ADRENAL SURGERY

Bleeding may be encountered during either OA or MIA. Anomalous vasculature may be present and, if not anticipated, may lead to significant bleeding. Castilho et al.[47] reported conversion of a laparoscopic procedure to open when an anomalous right adrenal vein was not recognized draining to the liver. When operating on the left adrenal, particular care should be taken to avoid injury to Belsey's artery, a communicating branch between the left gastric and inferior phrenic arteries. This vessel lies close to the esophageal hiatus, and is often accompanied by a phrenic vein.[48] When encountered, Belsey's artery, as well as any associated phrenic vessels, should be ligated to prevent avulsion.

Injury to adjacent organs may also occur during adrenalectomy, most commonly to the diaphragm and pleura. If recognized intraoperatively, the injury may be repaired without the need for thoracostomy tube placement. If such an injury occurs during OA, a red rubber catheter is placed through the defect, with the other end draining into a container of water. This defect is closed with a purse-string chromic suture during hyperinflation of the lung once no bubbles are seen exiting the water end of the catheter. The catheter is removed immediately prior to tightening the purse-string suture. Laparoscopic identification and suture repair of diaphragmatic injuries has also been reported.[49] In any case of diaphragmatic injury, a chest radiograph should be obtained postoperatively to evaluate for pneumothorax, and a thoracostomy tube may be placed at that time if necessary. Other adjacent organ injuries that may occur during adrenalectomy include capsular tears of the liver or spleen, which usually can be managed with a combination of manual tapenade, argon beam coagulation, and hemostatic gel packing.

Complications specific to the laparoscopic approach include trocar injury during placement and port site hernia. The passage of trocars should be done under direct vision; if inadvertent organ injury is suspected, close inspection and repair should be performed. Moreover, when exchanging instruments during the case, they should be passed under direct visual guidance. With regard to postoperative port site herniation, there is no consensus on the minimum port site size that necessitates closure; however, the need for closure of smaller port sites depends on both the size of the child and the type of trocar used.

SPECIAL CONSIDERATIONS

Neuroblastoma

Neuroblastoma is the most common extracranial solid tumor in children, with 1 case per 7000 live births. The adrenal gland is the origin of the tumor in 40% of the cases, which explains why neuroblastoma is a major cause of adrenalectomy in children.[15,50] The growth pattern of neuroblastoma can be variable, ranging from sharply demarcated tumors to highly infiltrative lesions. Likewise, the role of surgery in the management of neuroblastoma varies. Low-risk neuroblastoma may be eligible for surveillance, whereas localized tumors with favorable biologic factors can be cured with surgical resection. In advanced disease, resection is only one component of multimodal therapy. The often infiltrative growth pattern of neuroblastoma has led most surgeons to excise these tumors via open resection, with the choice of a transabdominal versus retroperitoneal approach guided by tumor location and adjacent organ involvement.

The role of MIA in neuroblastoma has been evolving over the past 15–20 years. In two large multicenter studies of pediatric neuroblastoma, Iwanaka et al.[16] and Leclair et al.[15] found that MIAs should be mainly performed in children with encapsulated masses and low-risk neuroblastomas, such as in young patients found with adrenal masses prenatally or in mass screening efforts. In a comparison of laparoscopic adrenalectomy with OA for pediatric adrenal neuroblastoma, Kelleher et al.[51] found that laparoscopic adrenalectomy could be safely performed with equivalent outcomes in patients with tumors smaller than 5 cm and without vascular encasement. Recent advances in technology and understanding of the disease have allowed for better assessments of tumor biology and risk stratification. The International Neuroblastoma Risk Group Task Force[52] developed a new staging system based on clinical criteria and IDRFs. Masses with IDRFs include masses that surround major vessels or nerves or invading structures, such as the spinal canal. Tumor histology and biology are also essential for risk stratification, including the presence of MYCN amplification, ploidy, and genomics.

In localized neuroblastoma without IDRFs (stage L1), the masses are suitable for primary resection with MIA as a feasible option if the tumor is well encapsulated. In neuroblastoma with IDRFs (stage L2), a biopsy of the mass gives information about the biology of the tumor. Patients with L2 neuroblastoma undergo neoadjuvant chemotherapy, and should then be reassessed after the chemotherapy. If all the surgical risk factors are negative (which includes having all the major vessels free of disease), and if the histologic features of the tumor are favorable, MIA may be safely utilized for treatment. Monclair et al.[53] have further shown that a select group of L2 patients with few IDRFs may safely undergo primary surgery with excellent overall survival. Regardless of the technique, it is essential to have a complete resection, as any remnant increases the risk of local recurrence.

The influence of local control by surgery or radiation therapy on overall survival in metastatic neuroblastoma (stage M) is controversial.[54] Englum et al.[55] have shown that in a cohort of children with high-risk neuroblastoma, the majority of whom had metastatic disease, resection of greater than 90% of the tumor was associated with improved overall survival. Children in complete remission or good partial remission of metastases after chemotherapy may benefit from local control. In children with metastatic neuroblastoma and no IDRFs, MIA may allow for a rapid postoperative recovery and immediate resumption of medical therapy, thereby minimizing the interruption of chemotherapy.

Pheochromocytoma

Pheochromocytomas are catecholamine-secreting tumors from the adrenal medulla. Approximately 10% of cases of pheochromocytoma occur in children, and 40% of pediatric patients with pheochromocytoma are associated with known genetic mutations.[56,57] Pheochromocytomas are characterized by catecholamine production; as such, the clinical manifestations of these tumors result from the physiologic effects of catecholamine excess.

Close cooperation of the pediatric urology, medicine, and anesthesiology teams is required in the management of patients with a pheochromocytoma. Patients are typically treated preoperatively with alpha-blockade (phenoxybenzamine) to control their blood pressure. Beta-blockers may be added to alpha-blockers to prevent arrhythmias, but beta-blockade administered without prior alpha-blockade may cause a significant increase in peripheral vascular resistance due to unopposed alpha-activity.[46] In addition, many patients have decreased intravascular volume, and therefore intravenous fluids are aggressively administered in the perioperative period to expand plasma volume and minimize intraoperative and postoperative hypotension. Severe intraoperative hemodynamic instability from catecholamine release may occur if the adrenal is manipulated. Early control and division of the main adrenal vein is essential in order to prevent the systemic release of catecholamines during dissection of the gland. Given the potential for blood pressure fluctuation, which may occur after ligation of the adrenal vein, the anesthesiologist should be notified at the time of adrenal vein division, and should be prepared to give intravenous fluids and vasopressors if needed.

Hereditary pheochromocytomas occur in von Hippel–Lindau (VHL) syndrome, multiple endocrine neoplasia (MEN) type 2, familial paraganglioma syndromes (succinate dehydrogenase gene mutations), and neurofibromatosis type 1. Hereditary pheochromocytomas, especially those with a mutation in succinate dehydrogenase B (SDHB), are often malignant and bilateral. MIA has been successfully used as the main treatment of choice for pheochromocytomas. The approach (TA, LRA, or PRA) depends on the size of the mass and experience of the surgical team. Two-thirds of children with an SDHB mutation have malignant tumors, so a total adrenalectomy is the best option. In VHL and MEN type 2, the risk of malignancy is low, so a partial adrenalectomy can be a viable alternative to prevent lifelong glucocorticoid and mineralocorticoid replacements and decrease the risk of metachronous tumor.[58] Volkin et al.[59] and Fallon et al.[60] have reported successful partial adrenalectomy in pediatric patients with VHL and pheochromocytomas via both open and minimally invasive approaches, with utilization of intraoperative ultrasound in minimally invasive cases. In adult patients with VHL, the recurrence rate was found to be close to 11%, with preservation of adrenal function in 90%.[58] For a partial adrenalectomy, the tumor pseudocapsule is identified, and the plane between the mass and normal adrenal gland is dissected out.

Congenital Adrenal Hyperplasia

Hugh Hampton Young first reported adrenalectomy as a treatment for congenital adrenal hyperplasia (CAH) in the 1930s.[61] With the development of synthetic adrenal steroids, however, the management of these patients has become almost exclusively medical (apart from genital reconstructive surgery). For most patients, the dosage of exogenous steroids needed to impede adrenal androgen production does not result in severe hypercortisolism with its associated sequelae. However, in some patients, suppression of adrenocorticotropic hormone (ACTH) is difficult, requiring large doses of exogenous steroids, which may cause obesity, hirsutism, acne, and other cushingoid features. In women, hypercortisolism may also result in menstrual irregularities, significant bone loss, and infertility.[62]

Van Wyk and Ritzen revisited the concept of adrenalectomy as a treatment for CAH patients who were difficult to manage on medical therapy.[63] In a study of 18 patients who underwent bilateral adrenalectomy for treatment of CAH and were followed an average of 59 months, virtually all patients had a significant decrease in androgen excess.[64] A separate investigation reported two women with CAH who had been infertile and oligomenorrheic who then experienced successful pregnancies following bilateral adrenalectomy.[65] Castillo et al.[66] reported a series of three patients with failure to respond to medical therapy who achieved either complete or partial regression of acne, hyperpigmentation, and virilization symptoms after bilateral MIA. In addition, although the majority of studies on adrenalectomy as a treatment for CAH have involved patients with 21-hydroxylase deficiency, patients with 11-beta-hydroxylase deficiency, who are prone to develop hypertension as part of the disease process, have also been treated with bilateral adrenalectomy, with a subsequent improvement in blood pressure.[63]

Lastly, whereas the aforementioned studies employed adrenalectomy as a treatment for CAH patients, the role of prophylactic adrenalectomy has been explored for patients with CAH as well.[62] Until longer-term data are available, however, prophylactic adrenalectomy is still considered experimental.

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Section 3

The Kidney

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CHAPTER 19

Basic Science of the Kidney

Heidi A. Stephany, John C. Thomas, and John C. Pope IV

INTRODUCTION

An attempt to define the term *translational* compared to deciphering a foreign language in that "getting the word right is relatively easy but getting the meaning of the word is much more difficult."[1] The process of translating basic science research to improvements in clinical patient care has revolutionized the way medicine is practiced in the late twentieth century and early twenty-first century. One example is in the area of renal transplantation. While the refinement of surgical technique has contributed to the overall success of the transplant, one must also recognize the monumental advances in immunobiology that have ultimately determined the long-term outcome of the allograft. These translational efforts have led to the development of immunosuppressive drugs capable of preventing allograft rejection in the patient. Just as this type of research has contributed to the success of renal transplantation, pediatric urologists and nephrologists are faced with the issue of finding ways to prevent certain anomalies in their patients that ultimately lead to renal failure and the need for transplantation.

In order to address this issue, clinicians must first have a general understanding of normal and abnormal molecular renal development. Second, while urinary obstruction, untreated neurogenic bladders, and vesicoureteral reflux (VUR) are just a few known disease processes that can lead to progressive renal damage, current research is focusing on ways to detect at-risk individuals in whom early intervention is beneficial. Understanding the pathophysiology of nephropathy at the cellular level can provide potential markers that could possibly alert the caregiver to a particular problem before renal damage occurs (Figure 19.1). Unfortunately, despite our best efforts, some children will continue to develop renal failure, necessitating renal replacement therapy, and better alternatives, such as tissue engineering of new organs, are actively being pursued.

This chapter briefly reviews the developmental biology of the kidney to highlight some of the more important regulatory factors involved in nephrogenesis. The pathophysiology of congenital obstructive nephropathy is used as an example to illustrate one congenital anomaly, particularly common in the urologic arena, whose ultimate aberrant molecular events can lead to end-stage renal disease. More importantly, it focuses on recent laboratory efforts that have elucidated numerous potential markers at the cellular level that play a role in the process of renal deterioration following insult to the developing kidney. Theoretic therapeutic options that act to inhibit or slow these damaging mechanisms, as well as potential alternatives to present renal replacement therapy, namely, tissue engineering and stem cell research, are also reviewed. Finally, a review of renal physiology is outlined, highlighting key factors relevant to the urologist.

Molecular Development of the Kidney

As the embryology of the kidney is addressed in Chapter 20, this section focuses on the numerous molecular signals that result in normal renal development. Formation of the kidney is a culmination of reciprocal inductive signals that occur between the ureteral bud and metanephric blastema. The bud develops from the Wolffian duct, and the mesonephric mesenchyme arises from intermediate mesoderm located in the caudal portion of the nephrogenic cord. Once these structures interact, the nephrons develop from mesenchymal transformation and the collecting system is formed from ureteral bud outgrowth and subsequent branching.

Since 2009, there have been more than 2900 genes implicated in genitourinary tract development, and they are cataloged in the Genitourinary Development Molecular Anatomy Project database (http://www.GUDMAP.org).[2,3] The goal of this project was to recognize molecular markers for the development of reporter mouse strains to further elucidate renal development.[4] Many of the major events in early renal development are controlled by highly conserved genes that regulate eye development in *Drosphila*.[5] The use of transgenic mice has generated much data concerning nephrogenesis, as manipulation of a specific gene can result in phenotypes consistent with human congenital anomalies of the kidney and urinary tract (CAKUT). Mesenchymal–epithelial transition (MET) is crucial for early renal development, as the pronephros becomes the definitive metanephros. One of the most important regulators of this early step is a transcription factor known as *PAX-2*. Mice homozygous for the *PAX-2* null mutation lack ureters, kidneys, and genital tracts, whereas heterozygous mice often form hypoplastic kidneys.[6] Also, these animals lack expression of *c-RET*, an important tyrosine kinase receptor expressed on the tips of the ureteral bud.[6,7] The *c-RET* receptor binds glial cell line–derived neurotrophic factor (GDNF), which is secreted from the developing mesenchyme. Ureteral buds in mice lacking *c-RET* expression fail to branch, whereas loss of GDNF results in apoptosis of the metanephric mesenchyme, both events

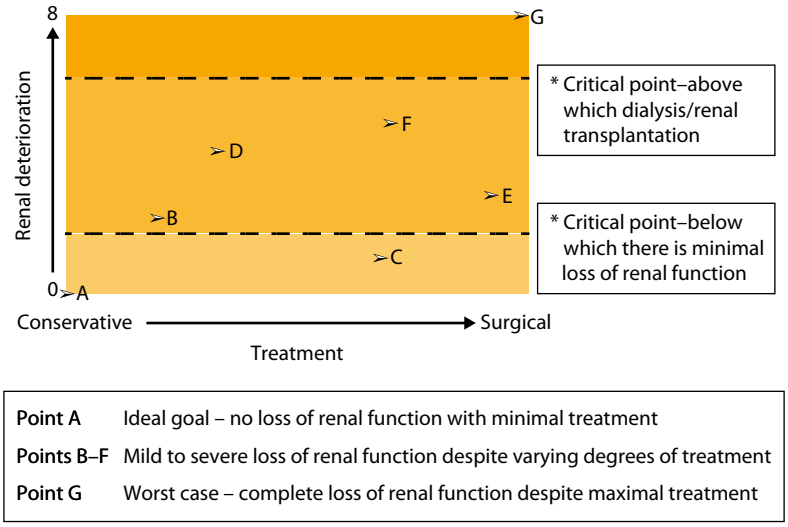

FIGURE 19.1 Schematic representation of current therapies and proposed novel approaches to treat kidney failure. (Reprinted from *Adv Drug Deliv Rev,* 63(4–5), Perin L, Da Sacco S, De Filippo RE, Regenerative medicine of the kidney, 379–87, Copyright 2011, with permission from Elsevier.)

leading to renal agenesis.[8,9] A similar phenotype is seen with mutations of upstream regulation of GDNF, namely, additional transcription factors, including *PAX-2*, *EYA-1*, and *WT-1*.[10,11] Mice lacking *EYA-1* or (*eyes absent*) lack expression of GDNF, whereas mutation of *WT-1*, which is expressed by uninduced mesenchyme, results in reduced expression of GDNF, although not enough to prevent renal agenesis.[8,10]

MET within the mesonephric mesenchyme occurs only following proper inductive signals from the invading ureteric bud. Once induction occurs, metanephric mesenchyme condenses at the tips of the branching bud to form mesenchymal aggregates. These aggregates epithelialize and begin the transformation from the vesicle stage, comma stage, and S-stage to ultimate fusion with the collecting duct, forming mature nephrons.[10] As condensation occurs, these cells express *WNT4*, an important glycoprotein exclusively found in kidney mesenchymal cells, which promotes MET through an autocrine activation mechanism. Nephrons in mice lacking *WNT4* fail to epithelialize.[12,13] Nephron maturation is also regulated by *BMP7*, a growth factor that is part of the transforming growth factor β (TGFβ) superfamily of signaling molecules. *BMP7* appears to operate downstream of other factors, like *WT-1*, *PAX-2*, *HNF1B*, and *WNT4*, and like *PAX-2*, it is expressed by both the mesenchyme and ureteral bud.[7] Homozygous mice with a mutation of *BMP7* have dysplastic kidneys that appear arrested in development and failure of mesenchymal induction, suggesting that *BMP7* may be a survival factor.[7,14] As mentioned, the TGFβ superfamily plays a role in kidney development, with *Gdf11* and *BMP4* necessary for outgrowth of the ureteric bud. One of the primary mediators of TGFβ signaling is *SMAD4*, and while collecting duct development is independent of *SMAD4*, removal of *SMAD4* causes impairment in the recruitment and organization of nephrogenic mesenchyme.[15] Further evidence supporting the importance of *SMAD4* has been demonstrated by the absence of canonical *SMAD4* signaling in ureteral mesenchyme leads to urothelial disorganization. *SMAD4* deficiency reduces the number and contractility of ureteral smooth muscle cells, and thus leads to a functional ureteropelvic junction obstruction (UPJO) secondary to abnormal peristalsis.[16]

Apoptosis plays a major role in the kidney, achieving its characteristic reniform shape. As certain areas of the undifferentiated mesenchyme (UMC) are destined to become crucial parts of the kidney, other cells undergo apoptosis. The renin–angiotensin system (RAS) plays a role in this process, mainly through the upregulation of the angiotensin types 1 and 2 (AT1 and AT2) receptors. The ligand for these receptors is angiotensin II, formed from the cleavage of angiotensin I by angiotensin-converting enzyme (ACE). Although AT1 receptors modulate renal vascular development and are found in more differentiated tissues of the kidney, AT2 receptors are expressed by UMC.[17] Mice with a null mutation of the AT2 receptor display phenotypes similar to those of human CAKUT, including VUR, UPJO, and duplicated collecting systems.[18,19] In vitro and in vivo studies show that angiotensin II promotes apoptosis of the UMC surrounding the developing urinary tract.[20] These studies suggest that mutations in AT2 can lead to untimely apoptosis of the UMC, potentially hindering not only the growth of the bud toward the mesenchyme, but also the diffusion of signals between these structures. Thus, the bud may develop from an ectopic location from the Wolffian duct and lead to VUR or renal hypo- or dysplasia.[21] Additional studies have demonstrated the importance of the interaction between the RAS and *c-RET*. Angiotensin II induces *c-RET* signaling and thus promotes ureteric bud branching.[22] Numerous other factors and genes are involved in renal development; however, this is beyond the scope of this section of the chapter. Table 19.1 shows other important genes involved in nephrogenesis. Some of the aforementioned genes, as well as others, are involved in more common syndromes seen clinically, which are listed in Table 19.2.[23]

TABLE 19.1 Genes involved in kidney development and the defect caused in mice lacking expression of the involved gene

Gene	Function	Homozygous loss in mice (–/–)[b]
WT-1[a]	Presence necessary for ureteral bud formation, precedes PAX2 and WNT-4 expression	Renal agenesis, absent ureteral bud formation
PAX-2[a]	Mesenchymal–epithelial conversion, expressed in ureteral bud, so probably has role	*PAX-2*$^{-/-}$ equals renal agenesis, absent ureteral bud formation; *PAX-2*$^{+/-}$ equals renal hypoplasia
WNT-4[a]	Morphogenesis of pretubular and tubular structures; mesenchymal–epithelial conversion	Small dysplastic kidneys
GDNF[a]	Ureteral bud formation; branching	Renal agenesis, absent ureteral bud formation
RET[a]	Receptor for GDNF-GDNFR-α complex, ureteral bud formation, and branching	Renal agenesis or tiny dysplastic kidneys
APC	Its protein product destabilizes β-catenin	In humans, mutations cause colon cancer
AT-1	Maturation of glomerular vessels, formation of renal pelvis	Absent renal pelves, immature glomeruli
AT-2	Mesenchymal cell apoptotic agent, has role in ureteral bud development	Congenital anomalies of kidneys and urinary tract
BCL-2	Prevents pre-epithelial, epithelial cell apoptosis	Renal agenesis, widespread apoptosis
BF-2	Present in mesenchymal cells that become stromal cells, persists in stromal cells, ureteral elongation, epithelial cell polarity	Short ureter, hypoplastic kidneys, incomplete rotation, renal fusion
BMP-4	Inhibits *WNT-11* activity, prevents ectopic ureteral bud formation, lengthens stalk of branches	*BMP-4*$^{-/-}$ equals congenital anomalies of kidneys and urinary tract
BMP-7	Prevents pre-epithelial cell apoptosis	Renal dysplasia
EMX-2	Ureteral bud branching, possible ureteral bud inducer of metanephric *WNT-4* expression, prevents pre-epithelial cell apoptosis	Renal agenesis, ureteral bud degeneration
EYA-1	May be inducer of GDNF expression and up-regulator of BCL-2	Renal agenesis, absent ureteral bud formation
FGF-2	Possible role in ureteral bud induction of mesenchymal–epithelial transformation	No published examples found
GDNFR-α	Auxillary receptor GDNF-α, ureteral bud formation; branching	Renal agenesis
IGF-II	Its protein product inhibits mesenchymal cell apoptosis	No published examples found
KAL-1	Specific role not known	In humans, mutation is associated with unilateral, bilateral renal agenesis
Ld	Ureteral bud formation	Renal agenesis or dysplasia, absent ureteral bud formation or penetration
LIF-1	Activates STAT-3, possible requirement for epithelial tubulogenesis, may stimulate *WNT-4* expression	No published examples found
LIM-1	Not known but likely has role in mesenchymal–epithelial conversion	Some have bilateral renal agenesis
PDGF-β	Mesangial cell formation	Absent mesangial cells
PKD-1	Protein product is polycystin-1, tubule morphogenesis, participates in cell-to-cell, and cell-to-extracellular adhesion bonds	Autosomal dominant polycystic kidney disease
PKD-2	Protein product is polycystin-2, translocates polycystin-1 to cell membrane	No published examples found
RAR	Likely inducer of Hox activity	Renal agenesis or dysplasia
SHH	May have role in ureteral bud induction of metanephric development	Hypoplastic kidneys, defective branching
VHL	Strengthens destabilizing bonds of glycogen synthase kinase-3, adenosine polyposis coli with β-catenin	In humans, mutation causes von Hippel-Lindau disease
WNT-11	Ureteral bud branching	No defects

Source: Reproduced with permission from Glassberg KI. *J Urol* 2002;167:2339–51.

[a] These genes may be focused on, but relative perceived importance of genes may change with time. Other genes are listed in alphabetical order. Some genes are not included in list and others have not yet been identified.

[b] Significance of each gene implied by the major defect that its absence causes.

Congenital Obstructive Nephropathy

Congenital obstructive nephropathy is but one of many developmental aberrations that occur in the kidney or urinary tract that can lead to renal injury and potentially renal failure. Ideally, the embryologic process of urinary tract development could ultimately be controlled so that these anomalies do not occur. Short of accomplishing this feat, it is critical to know which patients are at risk for renal injury and/or failure. If these patients could be

TABLE 19.2 Genetic disorders for human congenital anomalies of the kidney and urinary tract (CAKUT)

Gene (chromosome)	Gene product/function	Clinical syndrome	Phenotypes/symptom
PAX-2 (10q24–25)	Transcription factor	Renal–coloboma syndrome	Renal hypoplasia, solitary kidney, vesicoureteric reflux, optic nerve colobomas hearing loss
KAL (Xp22.3)	Anosmin1 protein functioning in neuronal migration and axonal targeting	Kallmann syndrome	Hypogonadotropic hypogonadism, anosmia, pes cavus, mirror movements of the hands, high arched palate, carebellar ataxia, renal agenesis/aplasia. Potter sequence. duplex systems, vesicoureteric reflux, lack of the vas deferens
EYA-1 (8q13.3)	Organogenesis	Branchio-oto-renal syndrome	Branchial cysts or fistulae, external ear malformation, preauricular pits, hearing loss cataracts, ocular anterior segment anomalies, unilateral renal agenesis with contralateral hypodysplasia, bilateral hypodysplasia, bilateral renal agenesis, ureteropelvic junction obstruction, vesicoureteral reflux, bifid kidneys
AGTR2 (Xq22–23)	Angiotensin II receptor type 2		Common CAKUT
HNF-1β (17cen-q21.3)	Hepatocyte nuclear factor-1β, organogenesis	Maturity-onset diabetes of the young	Young-onset non-insulin-dependent diabetes mellitus, renal cysts, hypoplastic glomerulocystic kidney disease, cystic renal dysplasia, solitary kidney, Mullerian anomalies

Source: Reproduced with permission from Nakanishi K, Yoshikawa N. *Pediatr Int* 2003;45:610–6.

identified early, it would theoretically be possible to slow or altogether prevent this deterioration in renal function.

Currently, there is significant controversy regarding the management of individuals with significant hydronephrosis based on the fact that hydronephrosis is not synonymous with obstruction.[24] Both nonoperative and early operative approaches have been advocated for infants with severe unilateral hydronephrosis.[25,26] Based on a more thorough understanding of the pathophysiology of renal fibrosis, the potential use of "biomarkers" may help to lessen this controversy. Biomarkers are defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathological processes, or pharmacologic responses to a therapeutic intervention."[27] Biomarkers for congenital obstructive nephropathy include anatomic details of the kidney gained through the use of imaging techniques, radionuclide scans to determine renal function, and microscopic analysis of biopsy specimens following obstruction.[27] The challenge faced by clinicians is learning how to use the information gained from these markers to direct appropriate care, such as timing of surgical intervention and medical treatment (i.e., administration of ACE inhibitors). The identification of biomarkers has been a popular area of research recently, and investigators have studied many urinary markers. One particular study examined the role of urinary epidermal growth factor (EGF), monocyte chemotactic protein-1, and β2-microglobulin, and found a significant correlation with tubulointerstitial damage in humans undergoing UPJO repair.[28] Urinary kidney injury molecule-1 and neutrophil gelatinase-associated lipocain have also been identified, and increasing levels are associated with worsening obstruction.[29] The ultimate goal for biomarkers in the pediatric urology arena is to recognize those patients at greatest risk for renal damage and providing appropriate intervention in a time-dependent manner to preserve and maintain renal function. While multiple studies have looked at potential biomarkers, the clinical application of various markers is still disputed.

Inconsistencies in the completion of nephrogenesis in various animal models have made it difficult to correlate postobstructive findings with those that occur in human obstructive nephropathy. Despite this shortcoming, animal models have contributed greatly to our understanding of fetal renal disease. These models consist of animals with spontaneous mutations or gene deletions (knockout), resulting in the desired phenotype, as well as surgically induced models of renal obstruction.[30] There is a broad spectrum of severity of obstruction in the human, and occult renal damage at the cellular level likely occurs prior to the development of hydronephrosis. Perhaps the most accurate model to demonstrate this is the neonatal rat, as only 10% of its nephrons are formed at birth, while the rest develop during the first week of life.[31] Thornhill et al. subjected the neonatal rat to partial unilateral ureteral obstruction (UUO).[32] In this study, renal growth decreased by 60% with a 70%–75% reduction in ureteral lumen, but much less when the lumen was reduced by ≤65%. Also, tubular atrophy and interstitial fibrosis correlated with tubular apoptosis and developed prior to renal pelvic dilation. Finally, persistent moderate partial UUO led to a marked decrease in ipsilateral glomerular filtration rate (GFR) and proteinuria before impairment of renal growth.[32] These findings carry extremely important clinical implications, as currently, no diagnostic test exists that allows one to reliably predict whether a hydronephrotic kidney is at risk for progressive renal injury at the cellular level.

Following the tireless efforts of numerous investigators, we now have a better understanding of normal renal development and the genes involved, along with the different mechanisms of renal damage following obstruction. Normal nephrogenesis includes increasing the number of nephrons and maturation of the renal vasculature,

glomeruli, tubules, and interstitium. This complex process involves the RAS and a balance between cellular proliferation and programmed cell death (apoptosis).[33,34] Significant obstruction can lead to impaired renal growth, resulting from tubular dilation and apoptosis, tubular atrophy, inflammatory infiltration of the interstitium, and unchecked accumulation of the extracellular matrix (ECM), all culminating in renal fibrosis and glomerulosclerosis.[27,35,36]

The following section outlines important mediators in fibrotic renal disease by briefly discussing their actions at the cellular level. Since other conditions seen clinically in pediatric urology can also result in renal fibrosis, these mediators can potentially be used as prognostic indicators of renal damage and be universally applied to multiple disease processes. Finally, once the role of these markers is understood, potential therapeutic options based on the activation or inhibition of their actions will be discussed.

TGFβ1

As mentioned, the TGFβ family is involved in many aspects of renal development and growth, but also has been implicated in fibrosis, particularly TGFβ1, which is a regulatory cytokine that is upregulated in response to tissue injury and can act synergistically with other growth factors to either inhibit or stimulate ECM deposition by recruiting fibroblasts.[37] Overaccumulation of ECM proteins, including fibronectin, collagen, and proteoglycans, as well as blocking matrix degradation by stimulating the action of protease inhibitors, results in fibrosis.[37–39] Tissue and urinary TGFβ1 has been shown to be increased in both animal and human models following urinary tract obstruction.[40–42] TGFβ exists as three isoforms (TGFβ1, TGFβ2, and TGFβ3), all capable of inducing fibrogenic effects on the obstructed kidney.[43] The main isoform is TGFβ1, and using immunohistochemistry in kidneys subjected to UUO, this cytokine has been localized to the renal tubules in the cortex and outer medulla, as well as from infiltrating macrophages in the interstitium.[44]

The complexity of TGFβ signaling is beyond the scope of this chapter, but initially, TGFβ binds the Type II serine/threonine kinase receptor, which then recruits and phosphorylates the Type I receptor, resulting in its activation. This receptor complex can then activate multiple signaling pathways, including RhoA, p38 mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase (PI3K), and the *SMAD* pathway.[45–48] Downstream phosphorylation of *SMAD2* results in the nuclear translocation of *SMAD2*, *3*, and *4* protein complexes.[49,50] *SMAD3* has been implicated in the fibrotic process through the activation of collagen promoters, downregulation of matrix-degrading enzymes, and upregulation of matrix metalloproteinase (MMP) inhibitors.[50,51] TGFβ1 also modulates the expression of microRNAs; in particular, it reduces the expression of mi-R-29, thus further promoting ECM deposition[52] In addition, TGFβ1 also drives epithelial–mesenchymal transition (EMT), which is characterized by tubular epithelial cell migration into the interstitium, where they are transformed into mesenchymal, myofibroblast-type cells. Renal tubular cells express fibroblast-specific protein-1 (FSP-1), which can be induced by TGFβ1 released by infiltrating macrophages or fibroblasts during renal injury. This activation allows certain epithelial cells to acquire mesenchymal migratory capacity and escape into the interstitium, where they facilitate deposition of interstitial ECM.[53–55] Recently, the role of EMT in fibrosis has been investigated, particularly looking at MMP-2. In MMP-2 knockout mice, less fibrosis was evident and there was a decreased amount of TGFβ and other EMT-related molecules, further suggesting the importance of EMT in progressive fibrosis in renal injury.[56]

TGFβ1 and its signaling pathways are major contributors to renal fibrosis following renal injury, and any of the numerous factors involved have the potential to serve as important biomarkers and therapeutic targets for subclinical renal injury following obstruction. If patients at risk for progressive renal fibrosis can be identified, then hopefully intervention can take place to slow, stop, or potentially reverse the fibrotic process. The significant advances in the laboratory deciphering all the many roles of TGFβ and downstream targets in fibrosis are daunting, yet numerous advances continue to promote further research.

Renin–Angiotensin System

In addition to TGFβ1, the RAS has also been implicated in the pathophysiology of renal fibrosis following obstruction. Along with regulation of renal growth, investigators have shown that the RAS plays a major role in the early response of a neonatal kidney following obstruction, and that reduced growth was secondary to decreased cellular proliferation and increased apoptosis.[57,58] Consistent with this early activation of the RAS in the neonatal kidney, there is a prompt and marked increase in ipsilateral renin mRNA following unilateral UUO with contralateral suppression of renin in the neonatal rat compared with adult rats. The persistence of an immature microvascular renin distribution, the presence of α-smooth muscle actin (α-SMA) in the peritubular capillaries, and the decreased total DNA content in the obstructed neonatal kidney all confirm the deleterious effects of obstruction in the developing kidney.[59,60] Angiotensin II directly increases the production of TGFβ and can induce fibrosis via a TGFβ-dependent or independent mechanism through direct activation of plasminogen activator inhibitor-1 (PAI-1).[61–69] PAI-1 promotes fibrosis by preventing the breakdown of plasminogen to plasmin.[63]

In vitro studies of oxidative stress on rat proximal tubular cells illustrate the role of angiotensin II in the promotion of cellular apoptosis. This is primarily mediated via the induction of TGFβ and generation of reactive oxygen species (ROS).[70] The RAS promotes normal renal development, but in cases of obstructive uropathy, it can promote fibrosis and accentuate renal injury through a variety of mechanisms. Consequently, therapies directed at inhibition of the RAS carry much promise in attenuating renal damage secondary to urinary tract obstruction.

Apoptosis

Following chronic ureteral obstruction, tubular and interstitial cells undergo programmed cell death, or apoptosis, all of which lead to renal tissue loss.[71–73] Once the inductive signal for apoptosis occurs, this leads to the recruitment

and activation of cytosolic enzymes called caspases (cysteinyl aspartate-specific proteinases). Using a mouse model of UUO, investigators showed a progressive increase in the activation of these caspases, namely, caspase-3, compared with sham-operated animals.[72] Apoptosis of both tubular and interstitial cells paralleled this increase in caspase expression.

Many signals, including growth factors, cytokines, ROS, and angiotensin II, can all initiate apoptosis. A neutralizing antibody to TGFβ ameliorated tubular apoptosis following UUO in the rat, while administration of enalapril, an ACE inhibitor, provided partial protection against tubular cell apoptosis.[74] Nuclear factor-κB (NF-κB) is an inducible transcription factor that upon translocation to the nucleus can induce the transcription of various genes, including *BCL-2* family members, angiotensinogen, and pro-inflammatory mediators, including tumor necrosis factor α (TNFα).[75] Angiotensin II and TNFα can stimulate further activation of NF-κB, reinforcing a positive feedback loop.[39] Increased vascular resistance following UUO causes transient ischemia and increased release of angiotensin II. Once obstruction is relieved, ischemia–reperfusion injury may result secondary to increased release of ROS, such as hydrogen peroxide (H_2O_2). Following UUO in mice lacking catalase, an enzyme capable of neutralizing H_2O_2, there was an increase in tubular epithelial cell apoptosis and interstitial fibrosis compared with wild-type mice.[76,77] Recent evidence has also examined the role of Paired box 2 (PAX2) in UUO and apoptosis. Compared with sham mice, TGFβ1, PAX2, collagen IV, and caspase-3 were all increased in the obstructed model, and the authors concluded that PAX2 is a potential therapeutic target in the prevention of renal fibrosis.[78]

Finally, evidence has linked nitric oxide (NO) as a possible protector against apoptosis. NO is produced by inducible nitric oxide synthase (iNOS), which is spontaneously expressed in the kidney. Using knockout mice lacking iNOS, investigators showed increased tubular cell apoptosis.[79] From a clinical standpoint, iNOS activity has also been shown to be elevated in children with UPJO, presumably induced by inflammatory cytokines, including TNFα and monocyte chemoattractant protein-1 (MCP-1), the latter also found in the urine of children with UPJO.[80,81] Further studies are needed, however, to evaluate NO as a prognostic indicator of recoverability of renal function following urinary obstruction.[79] One study looked at augmenting nitric oxide and suggested that decreasing iNOS activity contributes to decreased renal function in UUO, and animals transfected with the iNOS gene demonstrated improved renal function after obstruction.[82] With all the advancements made in the laboratory arena, investigators are hoping to find not only therapeutic interventions, but also biomarkers to decrease the invasive measures currently used to follow patients with potential for ensuing renal fibrosis or failure.[83,84]

The above were meant to highlight different signals and processes involved in progressive renal damage following obstruction. By no means is this an exhaustive description, as many other mechanisms have been implicated. Although presented separately, it is important to remember that these occur simultaneously, and that induction of one process may be dependent on another. This may have a therapeutic benefit, as inhibiting one signal or process can have the advantageous and additive effect of attenuating another.

Treatment Options

Renal fibrosis and atrophy secondary to various diseases are complex processes that have become more understandable in the last 15 years through the work of numerous investigators. Defining and detecting this process earlier may allow us to manipulate and possibly prevent renal damage by inhibiting a specific growth factor or cytokine, or blocking an entire pathway by interfering with upstream or downstream mediators.[85,86] As previously discussed, TGFβ plays a major role in renal fibrosis following obstruction. Potential treatment options include TGFβ neutralizing antibodies, antisense oligonucleotides, and blockade with a naturally occurring proteoglycan called decorin, all of which have limited ECM accumulation in vivo and in vitro.[74,87–89] Targeting the RAS with ACE inhibition and AT1 blockade results in impaired fibroblast proliferation, decreased myofibroblastic differentiation, and lowering of both TGFβ levels and NF-κB isotype activation. Of note, ACE inhibition also attenuated monocyte and macrophage infiltration.[90,91] Use of a direct renin inhibitor, approved by the Food and Drug Administration (FDA) in 2007, was also evaluated in unilateral obstruction and had anti-inflammatory and antifibrotic effects, despite an increase in renin expression, which was postulated to have suppressed receptor expression via negative feedback.[92,93] NF-κB is responsible for the upregulation of various cytokines, inflammatory mediators, and cell adhesion molecules, such as ICAM-1. Inhibition of NF-κB in rat kidneys subjected to UUO using an activation inhibitor called dehydroxymethylepoxyquinomicin (DHMEQ) showed less interstitial fibrosis and volume than obstructed controls.[94] *SMAD3*–deficient mice undergoing UUO showed decreased scar formation, less α-SMA staining in the interstitial fibroblasts, and decreased deposition of both collagen I and III.[95] Using a nephrotoxic nephritis model in the rat, treatment with a pan-caspase inhibitor decreased apoptosis, tubulointerstitial inflammation, and mRNA levels of collagen I, III, and IV.[96] Finally, because the role of MCP-1 has been firmly established as a pro-fibrotic modulator, blocking its receptor CCR2 also decreased fibrosis following UUO in a mouse model.[97]

EGF is also an important peptide whose manipulation has potential therapeutic ramifications following UUO.[98] EGF is produced by the ascending loop of Henle and distal convoluted tubule and modulates epithelial cell growth and metabolism, and plays a role in renal repair following injury.[81,99] EGF is decreased in the urine of children with congenital UPJO, while levels of MCP-1 are increased.[81] Following 5 days of UUO in the neonatal rat, the number of nephrons was decreased despite administration of exogenous EGF. However, tubular vimentin was decreased by one-third, and more importantly, tubular atrophy was reduced by 58% at 1 month following relief of UUO, an effect not seen in control animals.[100] In a similar study, exogenous EGF improved the decrease in renal blood flow in a partially obstructed ureteral

model.[101] Thus, administration of exogenous EGF could potentially slow the deleterious effects of obstruction on the maturing kidney.

Advances in Renal Replacement Therapy

Despite our best efforts, some children will still progress to renal failure secondary to various causes, including obstructive uropathy. Renal transplantation continues to be limited by an organ donation shortage, as well as the effects of organ rejection and the need for multiple organ transplants.[102] Numerous scientific advances in the fields of tissue engineering and stem cell research have given these patients hope that options other than organ transplantation may be available in their lifetimes (Figure 19.2).[103] Unfortunately, kidney reconstitution is difficult because in addition to excreting urine, there are many metabolic and endocrine functions of the kidney that maintain body homeostasis.[104] Stem cell therapy has been the headliner over the past few years, and significant advances have been made. Different sources of stem cells include embryonic and adipose tissue, and specifically for renal regeneration include bone marrow and amniotic fluid stem cells.[105] Animal models have shown recovery of renal function after injection, but how these cells are working has yet to be elucidated completely at this time.[106] As with any new treatment, long-term effects should not be overlooked, and this still remain unclear. While the use of stem cells and their advances in discovery may be potential therapies, questions still remain as to what type of stem cell and the best course of delivery.

Hammerman stated, "In order for glomerular filtration, reabsorption, and secretion of fluid and electrolytes to take place in a manner that will sustain life, the nephrons must be integrated in three dimensions with one another and with a collecting system and that vascularization must occur in a unique organ-specific manner from endothelial precursors that may originate from both inside and outside the developing renal anlage."[107] Initial studies confirmed that implantation of developing nephrons into the cortex of newborn mice resulted in differentiation and growth of the donor nephrons. Incorporation of these nephrons, however, into the host collecting system was not seen.[108,109] Studies have also shown that human fetal kidney tissue grafted under the renal capsule of immunodeficient rodents evoked a lower immune response compared with grafting adult renal tissue.[110] In addition, the fetal kidney has the potential to not only incorporate growing vessels from the developing abdominal aorta, but also attract its own vasculature in situ, which is important in terms of maintaining viability during transplantation.[111] Transplantation of a developing embryonic rat kidney into the omentum of an immunocompetent rat following unilateral nephrectomy resulted in increased renal growth, maturation of tubules and glomeruli, and incorporation of host blood supply from the superior mesenteric artery.[112] More importantly, survival in an anephric rat was prolonged to 7 days by this transplanted kidney.[113,114]

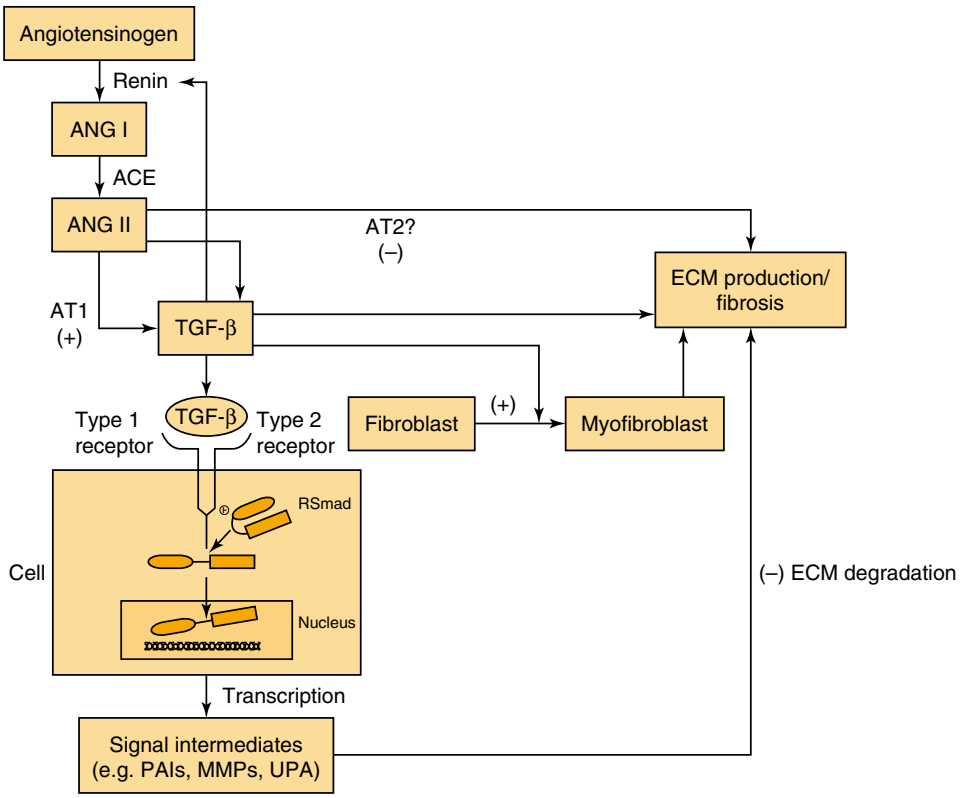

FIGURE 19.2 Summary of the roles played by the renin–angiotensin system, TGF-β, and TGF-β-downstream signal mediators in tissue fibrosis. ANG 1, ANG II, angiotensin I and II; ATI, AT2, angiotensin type 1 and 2 receptors; RSmad, receptor-activated *SMAD*; ECM, extracellular matrix; PAIs, plasminogen activator inhibitors; MMPs, matrix metalloproteinases; UPAs, urokinase-type plasminogen activators.

Finally, in an attempt to find a more physiologic, yet still extracorporeal, alternative to dialysis, Humes et al. developed an artificial kidney that maintained the metabolic, endocrinologic, and filtration demands in acutely uremic dogs.[114] This "kidney" consists of a synthetic hemofiltration cartridge with a renal tubule cell-assist device (RAD) in which human renal tubule cells have been grown to confluence along the inner surface of the hollow fibers.[114,115] A recent Phase I/II FDA-approved trial using this device in intensive care unit (ICU) patients with acute renal failure showed that this experimental therapy could be delivered safely for up to 24 hours.[115]

Based on the above examples, there clearly has been tremendous effort by investigators concerning research in organ replacement and regeneration. Ongoing research is needed in these areas, as they may someday represent viable alternatives to renal transplantation in humans.

Renal Physiology: The Basics

Much like basic science of the kidney, renal physiology is quite complex, and this will be a simple review targeting urologists as the primary audience and focusing on the basic fundamentals required in understanding various urologic conditions. The basic functioning unit of the kidney is the nephron, with tasks including filtration (most important), reabsorption, secretion, and excretion. The kidney receives approximately 20%–25% of cardiac output, and renal blood flow is directly proportional to the pressure difference between the renal artery and vein. As mentioned, filtration is the most important function of the kidney, and the GFR is 125 mL/min in males and 100 mL/min in females. GFR is a reflection of overall renal function, which includes regulating total body salt and water content, managing electrolytes, and eliminating waste of protein metabolism.[116,117] GFR is estimated with serum creatinine and blood urea nitrogen, but more accurate is the 24-hour creatinine clearance, as estimated by the Cockcroft–Gault formula: CrCl (mL/min) = ([40 – Age] × ([Ideal body weight in kg])/(Plasma creatinine [mg/dL × 72]) × 0.85 (women).[118,119]

The RAS has been a target in renal fibrosis after obstruction, and renin is secreted by macula densa cells in the kidney at the detection of decreased blood pressure.[120] The action of angiotensin II is to increase intravascular volume through vasoconstriction of the efferent arteriole, thus increasing blood pressure. In addition to acting on the central nervous system to increase antidiuretic hormone (ADH) from the posterior pituitary, it increases aldosterone secretion from the adrenal cortex.[121]

The renal tubule has two primary roles, to reabsorb and secrete substances, and each section has a different function. The proximal tubule is responsible for the majority of reabsorption (60%), including sodium, chloride, bicarbonate, and water. The loop of Henle's job is to reabsorb NaCl in excess of water to create a high interstitial osmolality, allowing maximal urinary concentration, known as the countercurrent multiplier. The distal tubule primarily reabsorbs calcium and sodium, and the collecting duct is for fine tubing, and reabsorption of water is regulated by vasopressin (ADH).[122]

Finally, renal physiology pertinent to the urologist would not be complete without briefly mentioning renal tubular acidosis (RTA). The most common form, RTA Type 1 (distal), poses the most significance to urologists, as these patients have approximately a 75% chance of developing stones. This results from impaired distal tubular excretion of H+, and thus patients will have hypokalemia, hyperchloremia, and a nonunion gap metabolic acidosis.[123] Urine will be alkaline with hypocitraturia and high calcium. Stones are typically calcium phosphate, and urine pH will be >5.5. Treatment is with oral alkalization and citrate. RTA Type 2 (proximal) patients do not have stones, as their citrate is normal and results from failure of bicarbonate reabsorption in the proximal tube. This is more common in children, and patients may have growth retardation and metabolic bone disease. Treatment is with sodium bicarbonate. Lastly, RTA Type 4 is secondary to impaired cation exchange in the distal tube, with decreased secretion of hydrogen and potassium; thus, this is the only type of RTA with hyperkalemia, and treatment is aimed at reducing potassium.

CONCLUSION

Prevention of nephropathy will continue to be a major focus of pediatric urology clinicians and researchers. The goal of this chapter was to identify and discuss general areas of importance where research of multiple types can make a clinical impact. However, the information given is only a snapshot of selected research contributions and in no way represents the vast and continuous efforts by other investigators in the field. The potential of molecular biomarkers to serve as prognostic indicators of cellular damage is at the forefront of renal research. As technology diversifies, new research opportunities will also continue to materialize. These may include the use of genetically engineered animal models, targeted gene therapies, or improved surgical procedures with miniaturized instrumentation or the use of robotic assistance.

Although currently we cannot prevent renal failure, research in the laboratory has given us valuable insight into normal and abnormal renal development, mechanisms underlying renal damage, and new ways to administer renal replacement therapy. Open communication between clinicians and researchers, as well as the increased training of physician-scientists, will help fuel future research possibilities. In the end, what is learned in the laboratory will continue to be translated into a better quality of life for our patients.

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CHAPTER 20

Renal Vasculature and Kidney

Steven E. Lerman, Irene M. McAleer, Alan L. Kaplan, and George W. Kaplan

The gross anatomic development of the primitive vasculature forms during the first three gestational weeks. Angioblasts form from mesenchymal cells that separate from the primary trophoblast at the same time as other mesoderm is forming. These angioblasts appear in the body stalk and form isolated vascular spaces or blood islands, which become lined with endothelium,[1] and the eventual growth and union of these isolated spaces form plexi that eventually unite to form a system of closed vessels. Mesenchyme laid down around the endothelium forms the intima, media, and adventitia of the vessels. Once this system of closed vessels is in place, any new vessels that arise are outgrowths of existing vessels. Definitive vessels arise by selection, enlargement, and differentiation. The selection of resulting channels occurs through inherited patterns and hemodynamic factors. Vasculogenesis factors, such as vascular endothelial growth factor (VEGF) and erythropoietin (EPO), have been extensively studied in various animal models, with studies ongoing to correlate with human embryogenesis and fetal placental angiogenesis.[2–4] Additionally, it is hypothesized that renal vasculature formation may depend on migration of renal tissue endothelial stem cells. This is opposed to how other organs, such as the placenta, develop, where the epithelial cells acquire the endothelial phenotype during formation, rather than by migration of endothelial stem cells themselves.[5] It is during this period that paired dorsal aortae arise. In addition, paired postcardinal veins form to return blood to the heart from the caudal end of the body via a common cardinal vein. The postcardinal veins develop as the mesonephroi vessels and run dorsal to mesonephroi. The previously paired dorsal aortae fuse at the level of the fourth thoracic vertebra to the fourth lumbar vertebra to form a single descending aorta in the fourth week. Lateral branches of the dorsal aorta appear during the fifth week. These irregularly segmented vessels supply those structures arising from the nephrotome region, specifically the mesonephros, gonads, metanephros, and suprarenal glands. The number of lateral branches is reduced during involution of the mesonephros, with the lateral branches ultimately becoming the inferior phrenic, adrenal, renal, and gonadal arteries.

During the sixth week, the inferior vena cava formation starts (Figure 20.1). Subcardinal veins develop ventromedial to the mesonephros and connect with each other and with the postcardinal veins. The posterior cardinal veins, which supply the mesonephric kidneys, ultimately disappear when the mesonephroi involute; remnants of the posterior cardinal veins will become the root of the azygos vein and the common iliac veins.[1] Supracardinal veins develop dorsomedially to the postcardinal veins and will replace them. This process continues during the sixth to the eighth week of gestation, until the formation of the inferior vena cava is complete. *Connections between the subcardinal veins persist as a common stem uniting the left renal vein, the left adrenal vein, and the left gonadal vein to the vena cava. The right subcardinal vein forms the inferior vena cava at the level of the renal veins and the vena cava cephalad to the renal veins; this explains why the right adrenal vein and the right gonadal vein drain directly into the inferior vena cava.* The right supracardinal vein also persists as the inferior vena cava below the renal veins; the left supracardinal vein disappears entirely.

Although there are many normal variations in renal arterial supply, most tend to be variations of the arrangement of five segmental arteries: posterior, upper anterior, middle anterior, apical, and inferior polar.[6] During renal ascent from the pelvis, the developing kidneys receive their blood supply from the vessels that are closest to them. Normal ascent stops where the kidneys meet the adrenal (suprarenal) glands. The blood supply to the kidneys initially comes from the common iliacs but will ultimately arise from branches off the aorta. Earlier blood vessels used during renal ascent will involute and disappear unless ascent is incomplete (Figure 20.2).[1] Accessory renal arteries arise if some precursors do not involute; most arise from the aorta either superiorly or inferiorly. Accessory arteries are present in about 25% of adult kidneys and are more common than accessory veins (Figure 20.3). Obstruction of the proximal ureter can occur if an inferiorly placed accessory artery is present and if that artery crosses over the ureter.

Persistence of the right subcardinal vein as the inferior vena cava rather than the supracardinal vein results in a retrocaval ureter. All reported cases of retrocaval ureter have been right-sided except when situs inversus is present.[7]

Retroiliac ureter is a rare anomaly that may result if the iliac artery should form from a ventral root of the umbilical artery rather than a segmental branch of the aorta, as it normally does in the fourth week.[8]

DEVELOPMENT OF THE NORMAL GLOMERULUS

The glomerulus develops when the metanephric mesochyme mesoderm induced by the ureteral bud forms S-shaped bodies, which will become the future nephrons.

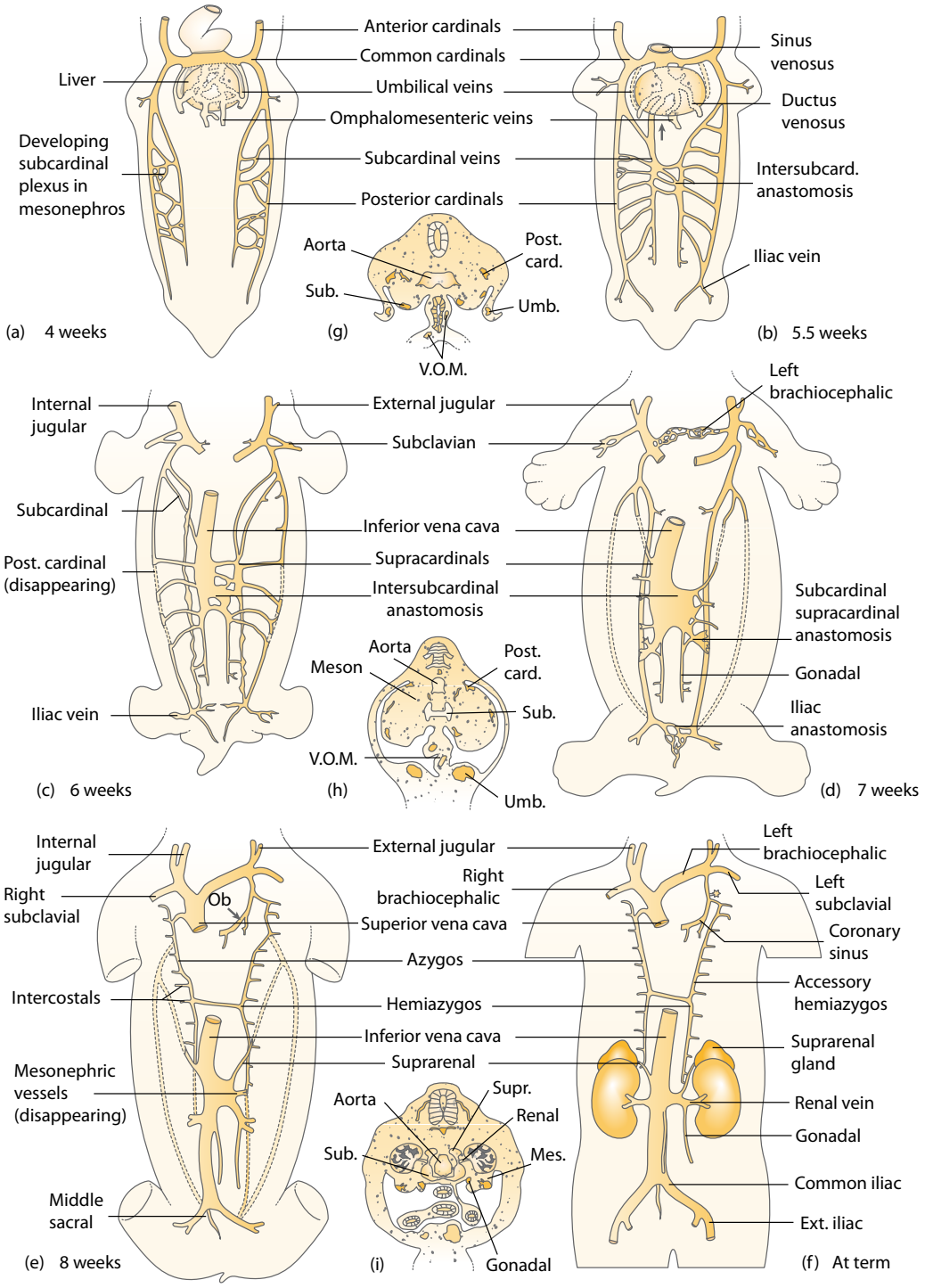

FIGURE 20.1 Development of the superior and inferior vena cava. (a–f) anterior views; (g–h) cross-sectional views. V.O.M., omphalomesenteric veins. (Adapted from Pattern W Jr. *Human Embryology*. New York: McGraw-Hill, 1976.)

These S-shaped structures are invaded by nearby blood vessels, forming the glomerular tuft. Glomerular formation occurs throughout gestation, starting sometime after 8 weeks, as demonstrated on immunohistochemical studies on autopsies done on fetuses from 8 weeks' until 40 weeks' gestation. Fonseca Ferraz et al. performed morphometric analyses on 86 fetal kidneys obtained during autopsy.[5] They found that nephrogenesis stopped between 32 and 36 weeks gestation. The nephrogenic zone, the area of the renal cortex that is closest to the capsule, where glomeruli present in S form, decreases with increased gestational age. As the nephrogenic zone decreased, the capillary tuft size of the intermediate glomeruli increased as well. This increase in the capillary tuft was not seen in the juxtamedullary or superficial glomeruli.[5]

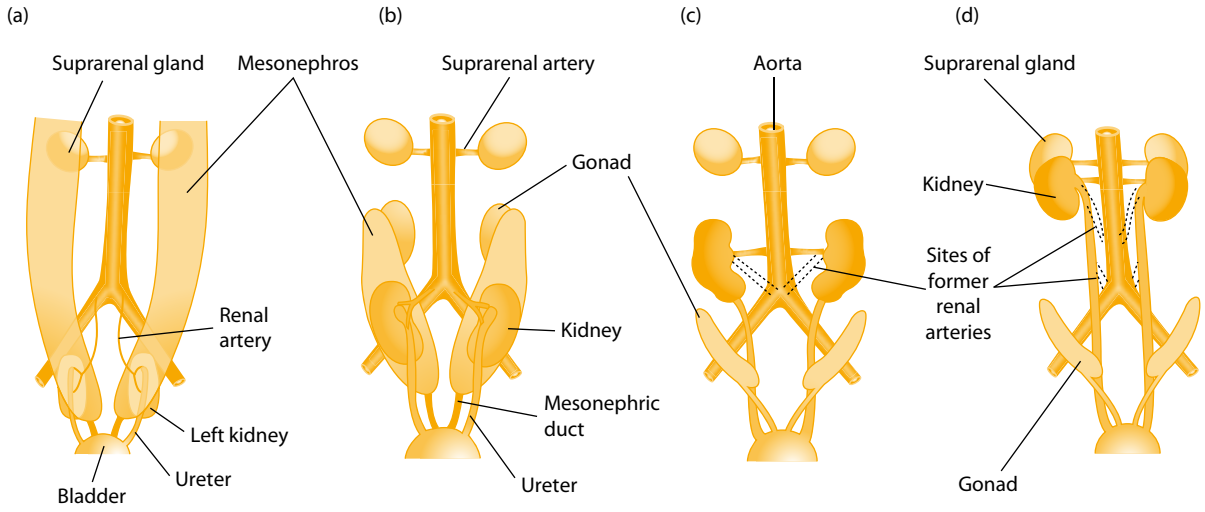

FIGURE 20.2 Ascent of the kidneys. (a–d) Diagrammatic ventral views of the abdominopelvic region of embryos and fetuses (6th–9th weeks) showing medial rotation and 'ascent' of the kidneys from the pelvis to the abdomen. (a and b) Observe also the size regression of the mesonephroi. (c and d) Note that as the kidneys 'ascend,' they are supplied by arteries at successively higher levels and that the hilum of the kidney (where the vessels and nerves enter) is eventually directed anteromedially. (Reproduced with permission from Moore KL, Persaud TVN. *The Developing Human: Clinically Oriented Embryology*, 7th edn. Philadelphia: Saunders, 2003.)

Wilms' tumor suppressor gene (WT1), which encodes a zinc finger transcription factor, is an important regulator of development of the metanephric kidneys. Kim et al. found WT1 in the developing glomeruli, in the comma and S-shaped bodies, and in the podocytes of the mature glomeruli. They postulate that the WT1 gene is required for the induction signal promoting the ureteral bud invasion of the metanephric mesenchyme. Many of the WT1 target genes were found to induct growth factor and membrane signaling pathways for renal development.[9]

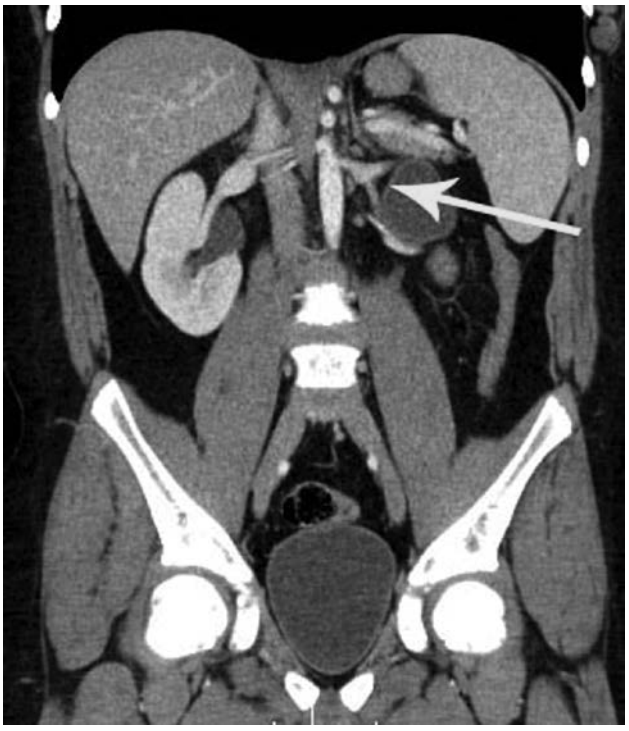

FIGURE 20.3 CT image of accessory crossing renal vessels causing ureteropelvic junction obstruction.

KIDNEY AND URETER

The urogenital system develops from the intermediate mesoderm arising from the dorsal body wall but will ultimately be ventrally located as a result of embryonic folding. This mesoderm arising on either side of the descending aorta will form the urogenital ridge. The urinary system starts developing before the genital system.[1]

There are three sets of kidneys that develop in mammalian embryogenesis. The first to form, during the first 21 days of development, are the pronephroi. These nonfunctioning units arise in the cervical and thoracic region of the embryo (Figure 20.4). The pronephros does not function in mammals but is analogous to the kidney in primitive fish. Seven pairs of tubules arise as dorsolateral sprouts from segmentally arranged nephrotomes (specialized areas of mesoderm). As the last tubule appears, the earliest is degenerating. The distal ends of these tubules bend dorsally, canalize, and unite one with another into a longitudinal collecting duct. This collecting duct eventually reaches the cloaca and communicates with it. The pronephric ducts persist and are necessary for the next interim kidney development. If the pronephros or its duct does not develop, the mesonephros will not form.

Late in the fourth gestational week, the mesonephros arises from nephrotomes caudal to the pronephros; these nephrotomes are unsegmented, unlike the pronephric nephrotomes. The mesonephric mesoderm separates into a longitudinal bar termed the nephrogenic cord. Within this cord, the mesenchyme forms into tubules. As one end of the tubule becomes associated with a knot of blood vessels, the other opens into the original pronephric duct, now called the mesonephric duct. With this process,

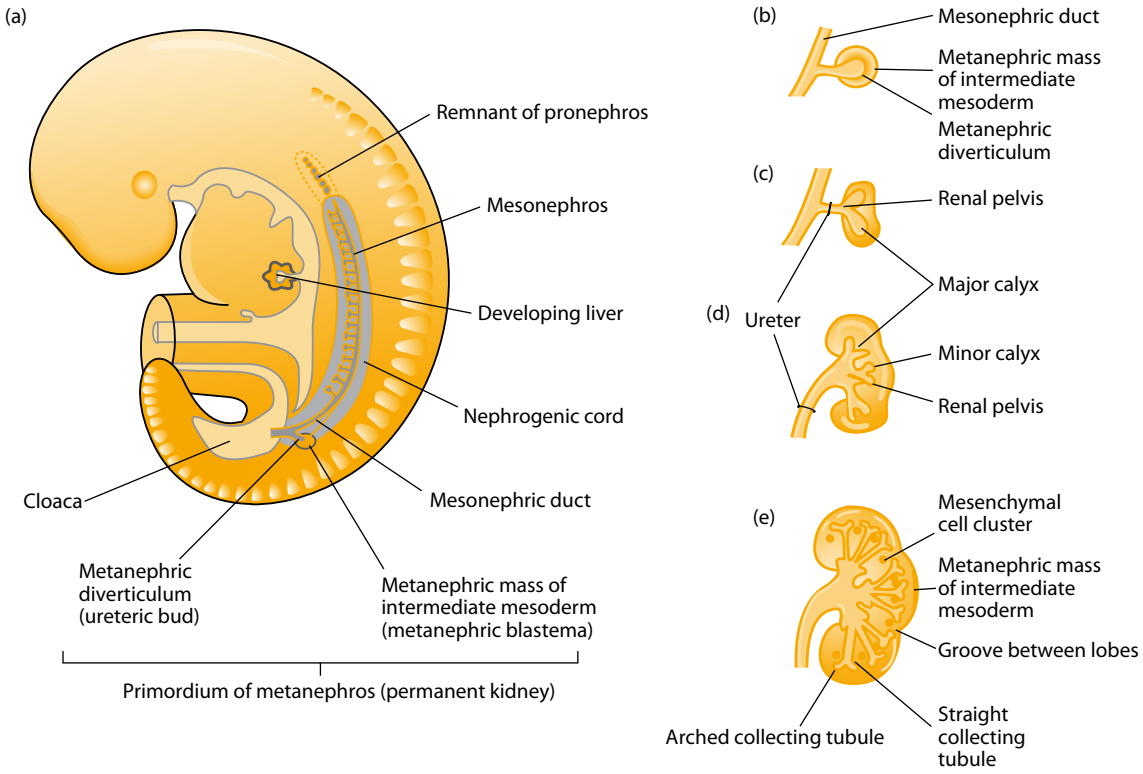

FIGURE 20.4 Development of the permanent kidney. (a) A lateral view of a 5-week embryo, showing the primordium of the metanephros. (*b–e*) Successive stages in the development of the metanephric diverticulum or ureteric bud (5th–8th weeks). Observe the development of the ureter, renal pelvis, calices, and collecting tubules. (Reproduced from Moore KL, Persaud TVN. *The Developing Human: Clinically Oriented Embryology*, 7th edn. Philadelphia: Saunders, 2003. With Permission.)

the nephrogenic cord becomes subdivided into spherical masses of cells that appear progressively from its cranial end to its caudal end. These masses will hollow and send out solid extensions that unite with the mesonephric duct. These solid extensions canalize and, with linear growth, bend into an S shape, forming the S-shaped bodies. Nearby tufts of capillaries form the glomerulus, which then indents the free end of the S-shaped tubule, becoming Bowman's capsule (Figure 20.5). Bowman's capsule and the glomerulus together make up the mesonephric corpuscle. Lateral branches of the aorta feed the glomerulus, while the postcardinal veins drain these tubules by sinusoids. The mesonephric tubules between the mesonephric duct and the glomerulus elongate and form a secretory segment and a collecting segment. As the tubules enlarge, the nephrogenic cord bulges into the coelom, forming a urogenital ridge on each side of the dorsal mesentery extending roughly from the diaphragm to the cloaca (Figure 20.6).

Programmed cell death, or apoptosis, occurs at set stages of renal development and is necessary for normal development and regression of the three forms of embryonic kidneys. Grossly, the pronephric tubules have completely degenerated by the fourth week, but the pronephric duct persists as the mesonephric (Wolffian) duct. The mesonephros begins to reach its stage of maximal development by the 28th day, with about 30 tubules in each mesonephros. The cranial tubules of the mesonephros degenerate, while others are forming caudally. Unlike the pronephroi, the mesonephroi are well developed and will function as interim kidneys for about 4 weeks. The glomeruli in animals studied (rabbits, cats, and pigs) can excrete ferrocyanide at this stage, while the tubules can secrete phenol red. At the caudal end of the nephrogenic cord, at the level of the sacral vertebrae deep in the pelvis, the metanephros soon appears as a metanephrogenic mass (nephric blastema).

The mesonephric duct makes a sharp bend before it enters the cloaca (Figure 20.4). The ureteric bud, which will become the ureter, renal pelvis, calices, and collecting ducts, arises from the dorsal medial aspect of this bend. It hollows and grows dorsally and then cephalad. It pushes into the metanephric blastema mass, composed of intermediate mesoderm, and separates from the nephrogenic cord. The interaction between the ureteric bud and the metanephric mass begins to induce nephrogenesis. The proximal end of the ureteric bud elongates to form the ureter, while the distal end, that portion pushing into the metanephrogenic mass, becomes the renal pelvis. The metanephric blastema mass surrounds the renal pelvis like a cap.

In the fifth week, early development of the permanent kidney is occurring, having been induced by the key union of the ureteric bud with the metanephrogenic mass. *The kidney is initially oriented in an anteroposterior direction, with the ureter entering the hilum of the kidney anteriorly* (Figure 20.2). With elongation of the ureter and straightening of the body, the kidney "ascends" from its pelvic position to its eventual normal site, just below the

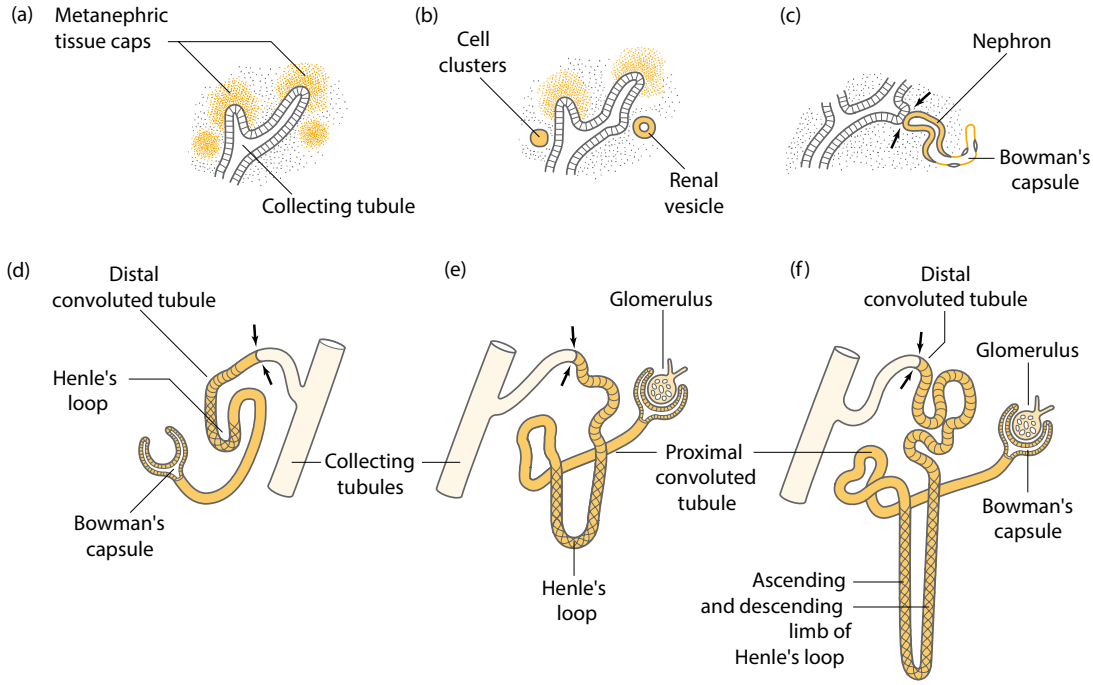

FIGURE 20.5 Development of a metanephric unit. Arrows indicate the place where the excretory unit establishes an open communication with the collecting system, thus allowing the flow of urine from the glomerulus into the collecting ducts.

suprarenal or adrenal glands; during the fifth week, however, the kidney is still caudal to the umbilical arteries. Late in the fifth week, the kidney begins to turn 90° on its vertical axis so that, ultimately, its dorsal border becomes its lateral border.

By the sixth week, the kidney has ascended sufficiently so that it lies cephalad to the umbilical artery. The renal pelvis flattens and divides into two major calices. By the seventh week, the kidney comes into contact with the suprarenal body and shortens and widens; by the eighth week, the center of the kidney has reached its permanent level opposite the second lumbar vertebra. The caudal pole is above the iliac vessels and the cranial pole below the suprarenal gland (Figure 20.2).

Cell proliferation is obviously also integral to renal development and differentiation. Ki-67 is a nuclear protein expressed in all stages of the cell cycle except for the resting phase and is used as a cell proliferation marker. Ki-67 is found in early metanephros development between 5 and 7 weeks. Measuring this protein increase during gestation weeks 5–7 shows the role of cell proliferation during branching of the ureteral bud and early nephron formation.

p53 genes and caspase-3 are found during apoptosis. Carev et al. found increased levels of these proteins and genes in the regressing mesonephros, as Ki-67 protein was found to increase in the developing metanephros.[10] The mesonephros completely regressed by the 16th week of gestation, as found by measuring p53 and caspase-3.[11]

From the 6th to the 20th week, the major calices progressively subdivide through 12 generations. The second, third, and fourth generations enlarge and fuse to form approximately nine minor calices. The fifth generation of

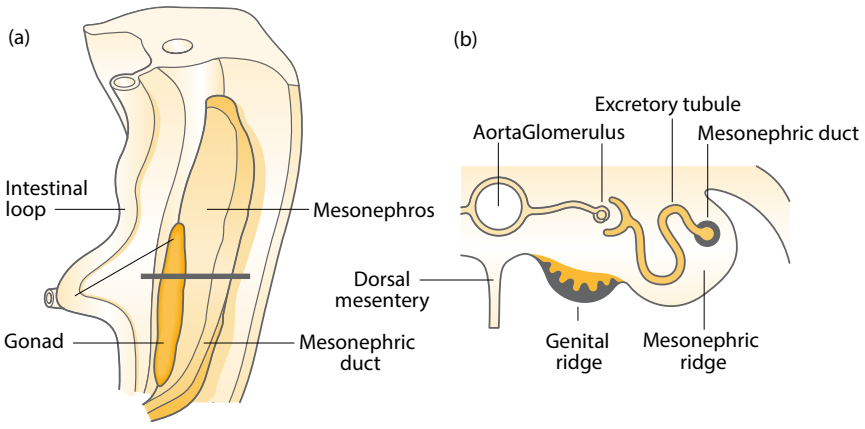

FIGURE 20.6 (a) Relationship of the genital ridge and the metanephros. Note the location of the mesonephric duct. (b) Transverse section through the mesonephros and genital ridge at the level indicated in (a).

branches (about 25 in number) form papillary ducts, emptying into the minor calices. The 6th to 12th branch generations form the collecting ducts in the renal medulla and project into the renal cortex. All the tubules draining into a minor calyx comprise a renal pyramid, the base of which adjoins the renal cortex, while its apex (papilla) projects into a calyx. The calices, pelvis, and ureter differentiate into transitional epithelium and become invested with smooth muscle and connective tissue by specialization of the surrounding mesenchyme during the eighth week.

The cap of metanephrogenic tissue that covers the ureteral bud has two layers: an external layer, which forms the renal capsule and connective tissue, and an inner layer, which forms the nephrons. The inner layer divides as the renal pelvis branches, so that a small cap of metanephrogenic tissue covers each subdivision through all 12 generations. As the renal cortex organizes, the region over each pyramid is demarcated from the next pyramid, so that as many as 20 lobes are formed. This lobation disappears progressively in infancy and early childhood but may be readily apparent on routine ultrasonographic examination as fetal lobulations, especially in infants.

During the seventh week, the inner layer of the metanephrogenic tissue begins to condense into spherical masses about the ends of the branches of the ureteral bud. These masses hang down into the angles between the branches. As the cortex thickens, new spheres form. The spheres change into vesicles and elongate, producing an S-shaped tubule, which unites with a collecting tubule. The blind end of the secretory tubule becomes the Bowman's capsule, while the midportion elongates and twists. An afferent arteriole grows in, the glomerulus differentiates, and an efferent arteriole grows out. The combination of the developing elongating metanephric vesicles that become the metanephric tubules and the glomerulus with Bowman's capsule ultimately form the nephron. Nephrogenesis starts in third-generation ureteral branches in the midportion of the kidney and in fifth-generation branches at the poles. *Nephrogenesis, or formation of nephrons, continues through the 36th week of gestation and then ceases. Although the number of nephrons does not increase with age, the size of the nephron increases throughout somatic growth.*

The fetal kidney is capable of secretion by the 10th week of gestation, and urine is produced. The bladder fills and urine is voided into the amniotic sac. The amniotic fluid is imbibed by the fetus and is an important factor in pulmonary maturation. A mature fetus can swallow several hundred milliliters a day, which is then absorbed by the fetal intestines. Fetal waste products are transferred through the placenta into the maternal circulation for disposal.

Scientific research has been quite extensive in human and animal models concerning the molecular control and triggering of embryonic development. Previously, normal renal development was thought to hinge on the metanephric diverticulum or ureteral bud making contact with the metanephric mass. Currently, embryonic renal development is thought to be due to signals from adjacent tissues, and coordination of normal organ development depends on appropriate interactions between constituent parts at the appropriate time for that development.[1]

Mesenchymal–epithelial interactions are crucial for the development of the branching organs, as in the kidneys, lungs, pancreas, and salivary glands. Molecular studies have shown that glial cell line–derived neurotrophic factor (GDNF), a transforming growth factor β (TGFβ), signals development of the ureteral formation and budding necessary to form the branching of the ureteral bud necessary for renal development. GDNF signals the branching using a receptor tyrosine kinase (Ret) and a glycophosphadidylinositol (GPI)-linked surface coreceptor, Gfrα1.

GDNF is expressed only in the metanephric mesenchyme adjacent to the caudal portion of the Wolffian duct, and Ret is expressed only at the distal tips of the ureteral bud. If GDNF, Ret, or Gfrα1 is absent, the ureteral bud will not form. About 40% of cases of renal agenesis in humans are found to be associated with Ret mutations and 5%–10% with GDNF mutations. Additionally, the formation of a single, appropriately located ureteral bud depends on correct GDNF regulation. GDNF also regulates restriction of budding of the Wolffian duct as to form a single ureter signaling the Sprouty 1 negative regulator enzyme[11] (Figure 20.7).

GDNF alone is not critical for branching of the ureteral bud, but GDNF triggering Ret, specifically located at the tips of the ureteral bud, allows for branching of the nephrons and collecting system. Sprouty 1 helps regulate the amount of branching as appropriate for the developing kidney. Ret signaled by Wolffian duct cells allows Ret active cells to move past other mesodermal cells in the Wolffian duct to form the first ureteral bud tip[12] (Figure 20.8).

The renin–angiotensin system also plays a critical role in the interaction between the ureteral bud and the metanephros. Angiotensin II (Ang II) also stimulates ureteral bud branching via c-Ret activation pathways. The absence or abnormal functioning of the pathways leads to aberrant ureteral bud development and branching, causing congenital abnormalities of the kidney and urinary tract (CAKUT).[13] CAKUT was coined by several urologists and nephrologists who found that there was divergence between the two communities concerning the causes of abnormal development of the kidneys and urinary tract. This combined system approach of nephrology and urology research concerning developing kidney pathways relating to the developing ureteral system pathways and their complementary effects may explain the various malformations that occur due to aberrant reciprocal induction in the urinary system.[14]

Major investigation in CAKUT has identified specific genes (PAX-2 and EYA1) responsible for the anomalies found in the developing kidney and ureteral bud.[15] Other molecules regulate nephron induction, such as TGFβ2 and bone morphometric proteins (BMP-7), and nephron maintenance and differentiation, such as fibroblast growth factor-2 (FGF-2) and leukemia inhibitory factor (LIF). Still other molecules, including PAX-2, BCL-2, ANG2 (Angiotensin 2), and hepatocyte growth factor (HGF), are thought to regulate apoptosis of the developing kidney tubules and nephrons.[1,16–18]

The PAX-2 gene was the first specific gene with a mutation found to be associated with CAKUT with high autosomal dominant penetrance.[19]

Multiple anomalies result from disordered embryogenesis of the ureter or kidney. Some are known to be familial, at least in some instances (e.g., ureteral duplications and vesicoureteral reflux [VUR]), whereas others are frequently associated with chromosomal abnormalities (e.g.,

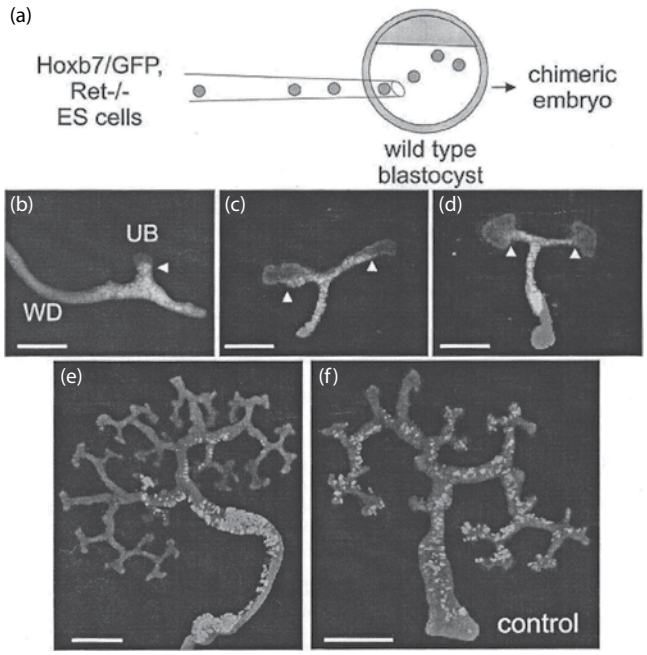

FIGURE 20.7 Inability of Ret$^{-/-}$ cells to contribute to ureteric bud tips in the kidneys of chimeric mice. (a) Generation of chimeric embryos. The embryos were recovered at different stages of ureteric bud outgrowth and branching, the mutant ureteric bud (UB) cells were identified by their expression of GFP, and the UB including wild-type cells was visualized by anti-cytokeratin staining. (b) At E11.0, Ret$^{-/-}$ cells contributed without restriction to the WD and to the trunk of the primary UB, but were excluded from the UB tip. The furthest point at which mutant cells were found is indicated by the white arrowheads. (c) After the first branching event (E11.5), the mutant cells had entered the two new branches, but did not extend all the way to the tips. (d) When the tips swelled to form ampullae, the mutant cells failed to contribute to the ampullae. (e) In an E11.5 kidney cultures for ~3 days, the mutant cells contributed to several generations of branches, but were absent from the more distal branches and all of the tips. (f) Control (Ret +/-, Hoxb7/GFP) ES cells contributed without restriction throughout the ureteric bud tips and trunks. Scale bars, 0.25 mm. (Panels [b-f] Reprinted from *Dev Cell*, 8, Snakya R, Watanabe T, Costantini F. The role of GDNF/Ret signaling in ureteric bud cell fate and branching morphogenesis, 65-74. Copyright 2005, with permission from Elsevier; from Costantini F, Shakya R. *Bioessays* 2006;28:123. With permission.)

horseshoe kidney and Turner syndrome). Most, however, seem sporadic in incidence.

If the pronephrosis fails to develop, the mesonephros will not develop; the result is renal and ureteral agenesis. Unilateral renal agenesis occurs in approximately 1 in 1000 newborns. Males predominate in occurrence, as does a proclivity to the absent kidney being on the left. Additionally, in the male, the ipsilateral genital ducts do not form. *Hence, there is a high association of renal agenesis in patients with congenital absence of the vas deferens.*[20] A similar situation would result if the mesonephric duct failed; however, if the mesonephric duct developed but the mesonephros did not, the kidney would be absent, while the genital ducts, and perhaps a blind-ending ureter, could result. If both kidneys fail to develop, oligohydramnios (due to a lack of fetal urine) produces the deformation

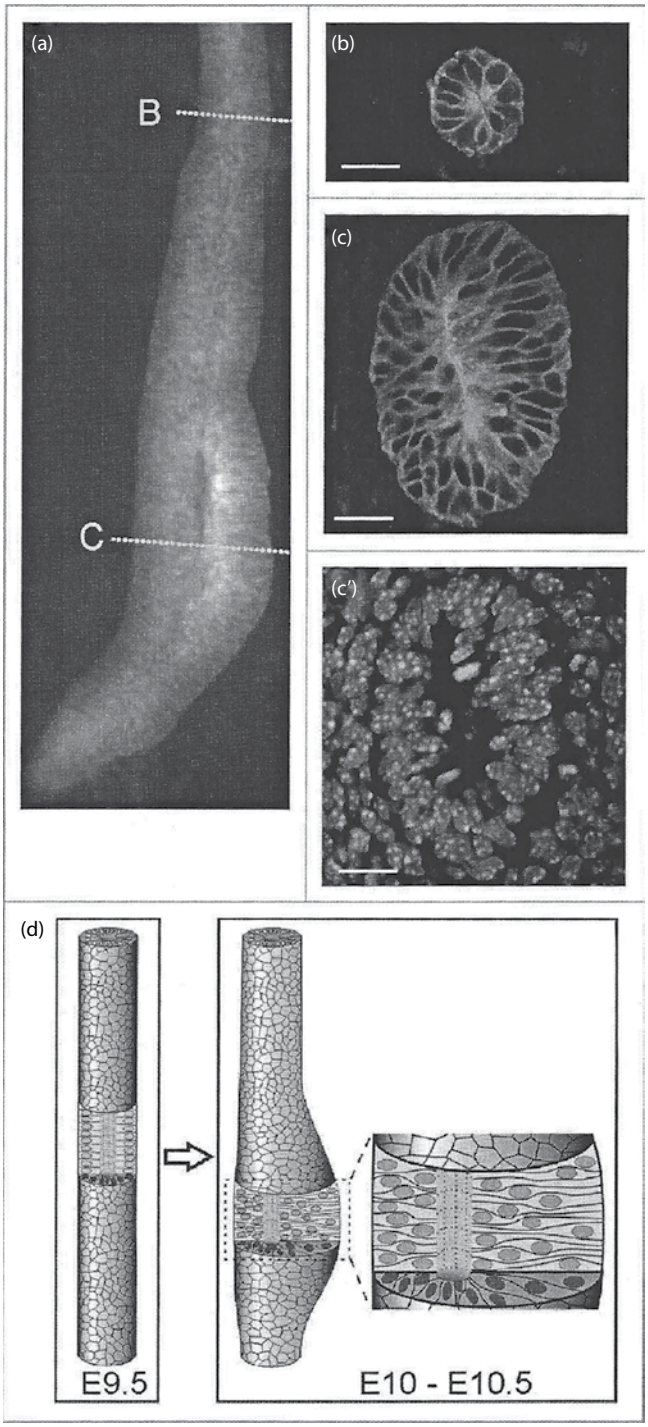

FIGURE 20.8 The nephric duct forms a transiently pseudostratified epithelium before ureteric bud (UB) formation. (a) Whole mount image of wild-type Nephric duct carrying *Hoxb7/myr-Venus* transgene at E10.0. Dotted lines indicate approximate planes of the sections at right, which show rostral ND in (B) and pseudostratified caudal ND in (C). (b and c) were stained with anti-GFP to detect myr-Venus and anti-pH3. (c') Hoechst nuclear stain of the section in (c). (d) Schematic diagram of the formation of pseudostratified epithelium preceding ureteric budding. The pseudostratified epithelium persists during early UB branching, but reverts to a simple epithelium before E14.5. (From Costantini F. *Organogenesis* 2010;6(4):258. With permission.)

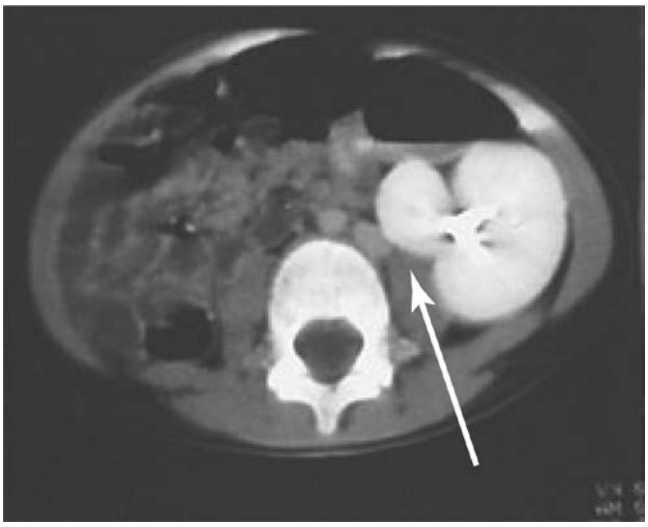

FIGURE 20.9 CT image of supernumerary kidney.

characteristic of Potter syndrome (characteristic facies with low-set ears, hypertelorism, and flattened nose, as well as limb deformities due to the relative absence of amniotic fluid) and interferes with pulmonary maturation. Occurrence of bilateral renal agenesis is approximately 1 in 3000 live births and is incompatible with postnatal life. Skinner and associates studied human DNA in 33 stillborn fetuses with renal aplasia or severe dysplasia and found Ret mutations in 37% of fetuses with bilateral renal agenesis and in 20% of the fetuses with unilateral renal agenesis. Interestingly, despite the GDNF–Ret association, it is rare to find abnormal renal development due to GDNF mutations. Of note, Ret mutations are also found in patients with Hirschsprung disease.[21]

Failure of renal ascent results in simple pelvic ectopia. Further ascent but failure of rotation is seen clinically as malrotation or incomplete rotation maintaining the normal embryonic anteriorly placed renal pelvis, or overrotation with either a laterally or posteriorly placed renal hilum. Many of these kidneys are also ectopically located. If the two metanephrogenic masses come into contact in the pelvis, they could fuse and form a pancake (lump) kidney. Fusion slightly later, usually in the lower pole of the developing kidneys, might result in a horseshoe kidney. The ascent of the horseshoe kidney is arrested by the inferior mesenteric artery. Horseshoe kidneys occur in about 1 in 500 people. These kidneys have a two to eight times higher risk for Wilms' tumor development than in the general population. The embryogenesis of crossed ectopia is harder to explain, but it may result from lateral bending and rotation of the tail of the embryo, thereby altering the course of ascent. In this way, both ureteral buds might penetrate a single metanephrogenic mass.[22] Supernumerary kidney formation is relatively rare. Formation of this anomaly is due to the division of the ipsilateral ureteral bud (Figure 20.9).

Cystic renal disease can occur with inherited conditions or through disruptions in normal development.

Autosomal recessive polycystic kidney disease (ARPKD) is a recessively inherited autosomal disorder that is reported to occur in 1 out of 6000–14,000 pregnancies. These kidneys are quite large and may replace most of the retroperitoneum. The cysts are due to enlargement of the collecting ducts; associated liver disorders with periportal hepatic fibrosis are also seen with this disorder. Those infants who do not survive infancy expire due to renal or pulmonary failure. Imaging of ARPKD kidneys with ultrasonography or postnatal computed tomography (CT) is characterized by very large kidneys with a streaking sunburst pattern (Figure 20.10).

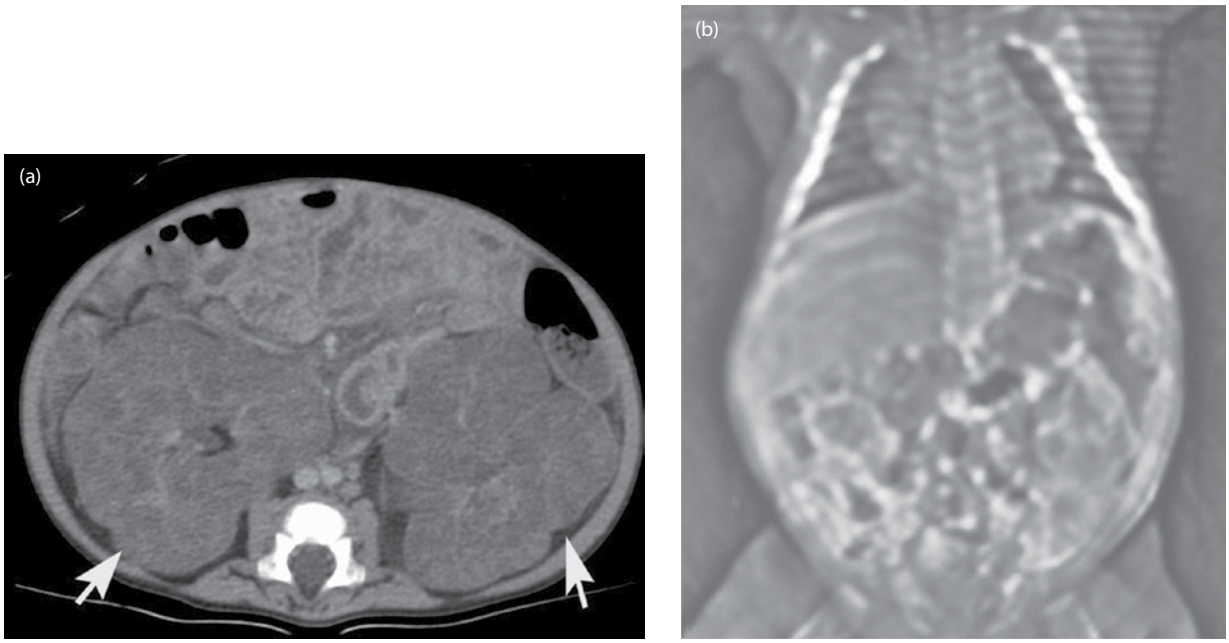

FIGURE 20.10 (a) CT image of ARPKD: note sunburst streaking pattern (arrows). (b) Composite image on CT demonstrates a large abdomen.

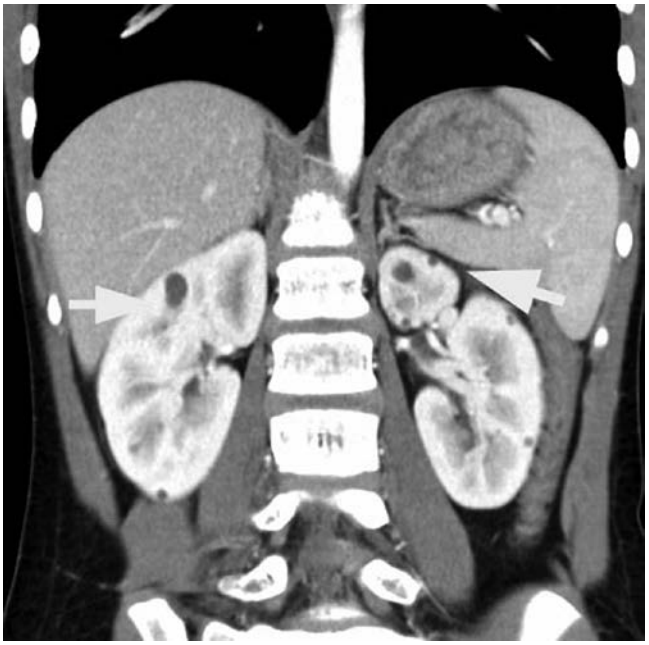

FIGURE 20.11 CT image of ADPKD.

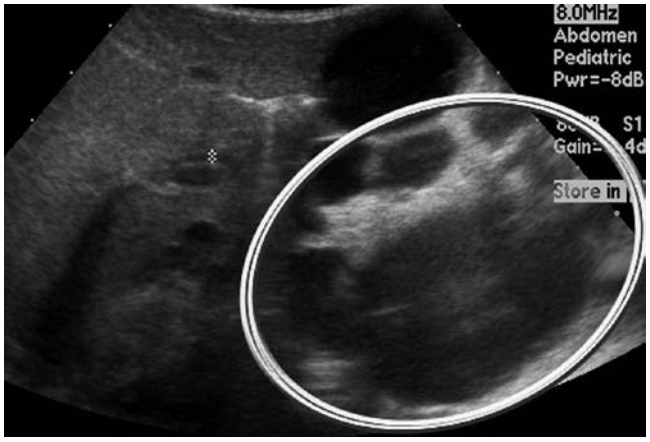

FIGURE 20.12 Ultrasound image of MCDKD.

Autosomal dominant polycystic kidney disease (ADPKD), which is more common than the recessive form, is characterized by cysts forming through abnormal branching of the collecting ducts, as well as cysts forming in other portions of the tubules (Figure 20.11).

Multicystic dysplastic kidney disease (MCDKD) has been said to result from early ureteral obstruction[23] or may result from disordered induction of the metanephrogenic mass by a faulty ureteral bud (Figure 20.12).[24] Complete involution of the cystic components of the multicystic kidney also accounts for some cases of renal agenesis. MCDKD is the most common form of cystic disease, with a frequency of 1 in 3000 pregnancies. In this disorder, there is no recognizable renal tissue present on gross examination, but there may be some dysplastic renal tissue interspersed with the cystic elements. Bilateral MCDKD is incompatible with life, but approximately 75% of cases are found with unilateral MCDKD involvement. These kidneys can be found with antenatal ultrasonography (Figure 20.9). Cysts in this case are thought to be due to dilations of the tubules, especially the loops of Henle.

Embryonic development theory suggests that normal nephrogenesis is dependent on the ureteral bud meeting the center of the metanephrogenic mass so that nephrogenesis is induced by the ureter.[25,26] Should they not meet at all, a blind-ending ureter would result. However, should they meet in an abnormal (degenerating) part of the metanephrogenic mass, renal dysplasia would be anticipated.[26,27] Pathogenesis of dysplastic kidneys has been studied extensively using animal models of urinary tract obstruction at various times in fetal gestation. Kitagawa et al. developed a model for MCKD by ligating fetal lamb urethras at various times during gestation. They found a dysplastic kidney to be pathologically similar to a multicystic kidney when the urethras were ligated at 60 days' gestation, well after the glomeruli started producing urine.[28] Recent human fetal tissue studies using three-dimensional histologic analysis theorize other etiologies for renal dysplasia from urinary tract obstruction causing two different types of dysplasia, MCDKD models and obstructive renal disease models, rather than the abnormal induction of the metanephric mass by the ureteral bud. Shibata and Nagata used human fetal renal tissue and felt that the cystic dysplasia occurred earlier in gestation in MCDKD since cystic areas appeared to decrease with increased gestational age, while interstitial dysplastic tissue increased with later gestational age. They found that cysts were more peripherally located with obstructive renal disease, and the rest of the kidney architecture was generally normal. They theorize that these cysts developed later in gestation because the effect of obstruction of the urinary tract occurs lower and must affect the urethra, bladder, ureter, or renal pelvis before it affects the developing nephrons. In MCDKDs, the obstruction is associated with pyelocalyceal obstruction, which is much higher in the urinary tract, and therefore will have an earlier dysplastic effect on the kidney.[29,30]

Congenital urinary tract obstruction develops with errors in induction of the metanephros and formation of urinary drainage, and through faulty maturation of the pyeloureteral peristaltic mechanism. Generally, anomalies in ureteral bud position, number, and abnormal connections between the ureter and the bladder lead to urinary tract obstruction. Defects in development of the kidney are primarily responsible for urinary tract obstruction, but abnormal remodeling of the lower urinary tract may also be responsible for lower urinary tract anomalies (VUR and ureterovesical obstruction). Faulty development of the pyeloureteral pacemaker cells may lead to ureteral obstruction by failure of unidirectional peristalsis allowing appropriate drainage of the upper urinary tract down the ureter to the bladder[31] (Figures 20.13 and 20.14).

Sonic hedgehog (Shh) gene inactivation is also responsible for defective ureteral mesenchymal differentiation with resultant hydroureter.

Recently, the focus of abnormal urinary tract development has been on associated progressive renal deterioration and renal failure in childhood and adulthood. Dysmorphic kidneys associated with VUR were thought to be due to sterile reflux. Reviews of ultrasonographic and renal scintigraphy without infection make inherent renal dysmorphism during development a more likely causative factor for the defects found. Furthermore, it has been found in

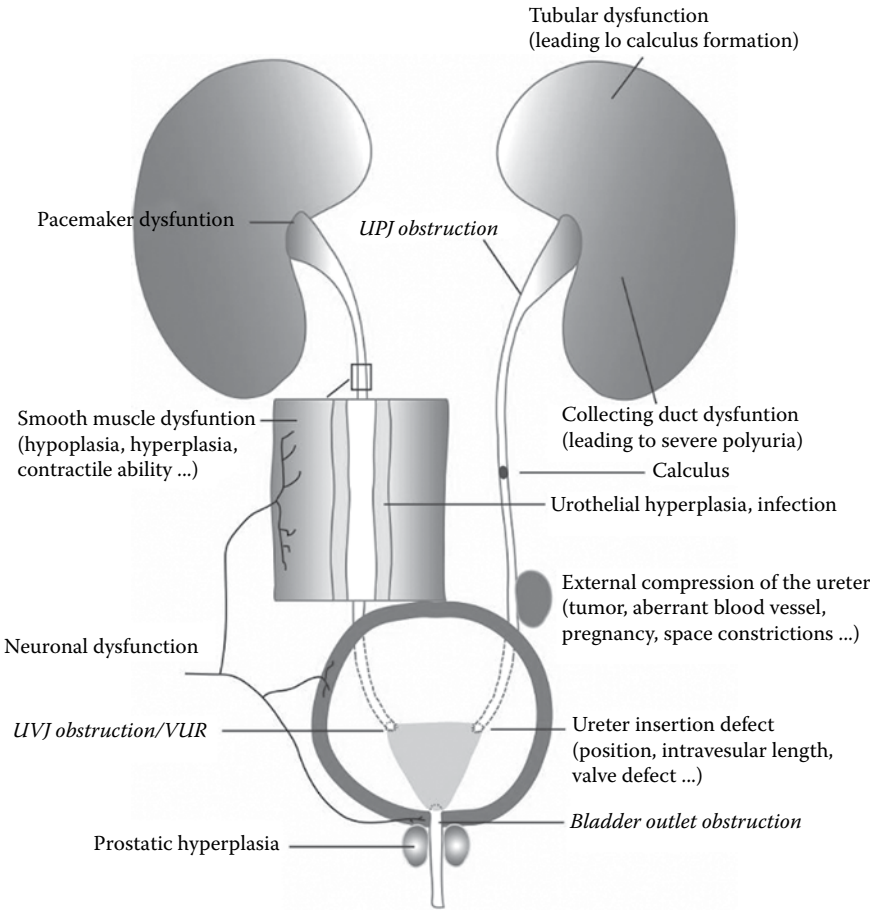

FIGURE 20.13 Causative factors for urinary tract obstruction. UPJ, UVJ and bladder outlet obstruction are in italics as these terms describe the location but not the causes for the obstruction. (From Chen F. *Pediatr Nephrol* 2009;24(9):1621–32. With permission.)

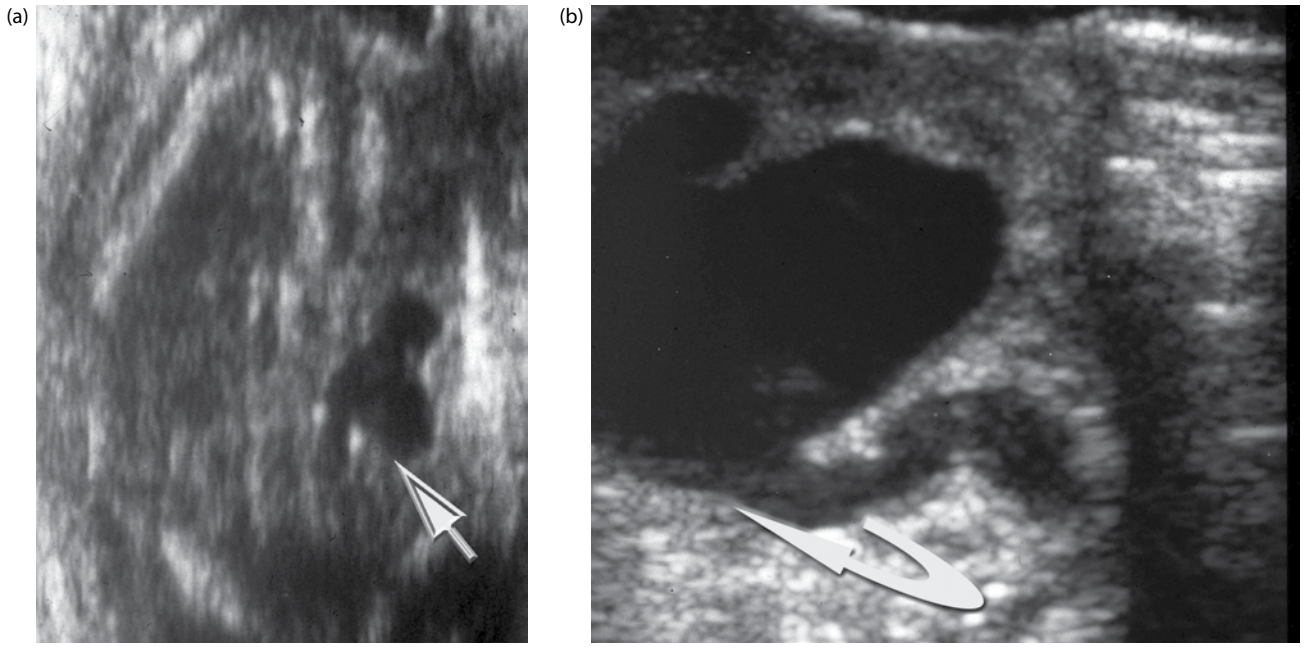

FIGURE 20.14 Prenatal hydronephrosis. (a) Arrow pointing to hydronephrotic kidney and prenatal hydroureter. (b) Arrow pointing from ureter to bladder.

animal studies that an initial critical reduction in renal mass will ultimately lead to progressive deterioration of renal function in the remaining renal tissue. CAKUT has been associated with oligonephronia of the contralateral kidney, especially accompanied by VUR.[19]

Hershkovitz et al. found that chronic hypertension and renal disease have been associated in low-birth-weight (LBW) infants, primarily due to prematurity and intrauteral growth restriction (IUGR).[32] Although many LBW infants catch up in growth, their kidneys, due to impaired and incomplete renal growth from IUGR and prematurity, have a lower than expected nephron number that does not improve with renal growth catch-up. They postulated that lifelong renal maintenance is dependent on the number of renal cell divisions, which in turn depends on normal fetal renal development. The cellular mass of the developing kidney depends on a balance between cell proliferation and apoptosis. Animal models have shown that IUGR is associated with higher levels of renal cellular apoptosis. Additionally, the renin–angiotensin system was found to be downregulated in the animal models studied. The authors also found that lower renal donor nephron mass increased the risk of the transplant recipient developing hypertension and transplant loss. Adults with a history of LBW and catch-up renal growth had a higher association of developing hypertension and renal disease.

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CHAPTER 21

Renal Anomalies

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INTRODUCTION

Congenital anomalies of the upper urinary tract comprise a diverse group of abnormalities and may be the result of an arrest in development or a malformation. These diverse entities are among the most common malformations in newborns. Using real-time ultrasonography (US) as a screening test in nearly 18,000 healthy infants, Calulo et al. found that nearly 1% had some type of a congenital anomaly of the kidney and urinary tract (CAKUT), and one-quarter of these required surgical intervention.[1] In a similar study of 5700 Asian infants that were screened over a 7-year period, nearly 200 cases (3.5%) of CAKUT were identified.[2] A complete understanding of the embryologic development of the genitourinary tract is a prerequisite for the evaluation of a child with a suspected anomaly.

EMBRYOLOGY

There are three stages in the formation of the nephric system: the pronephros, the mesonephros, and the metanephros. Embryologically, all three kidneys develop from the intermediate mesoderm. The two intermediate stages are the pronephros, which completely disappears, and the mesonephros. Although the mesonephros undergoes degeneration, its duct persists and extends caudally to communicate with the anterior cloaca. As the ducts fuse with the cloaca, canalization progresses both cranially and caudally, with the cranial extent transforming the solid tissue condensations into the definitive nephric ducts with excretory capability. Vestigial remnants of the mesonephric tubules occur in both sexes and are associated with the reproductive tract. In males, some of the mesonephric tubules become the efferent ductules of the testes. The epididymis and vas deferens are also formed from the mesonephric (i.e., Wolffian) ducts. In females, remnants of the mesonephric ducts form vestigial mesosalpingeal structures called epoophoron and paroophoron.

Early in the fourth to fifth weeks, the ureteral bud begins to develop from the distal end of the mesonephric duct near its junction with the cloaca. The cranial end of the ureter then ascends to meet the condensing blastema of the metanephric mesenchyme in the sacral region. This begins to develop into the metanephros and continues its cephalad migration. The cranial end of the ureteral bud begins a series of branchings to form the renal pelvis, the calyces, and a portion of the collecting ducts. This branching is associated with the simultaneous differentiation of the metanephrogenic cap, which becomes arranged around the branching collecting ducts, giving the metanephros a lobulated appearance. The nephron, which consists of the glomerulus, proximal tubule, loop of Henle, and distal tubule, derives from the metanephric mesenchyme. The collecting system, consisting of the collecting ducts, calyces, pelvis, and ureter, is formed from the ureteric bud.

The ascent of the kidneys occurs in part due to true migration and also secondary to differential somatic growth of the lumbar portion of the body. They reach their final level by the end of the eighth week of fetal life. The kidney also undergoes axial rotation medially of 90° during the seventh and eighth weeks before it assumes its final position. During ascent, each kidney receives its blood supply from the neighboring vessels. Initially, this is from the middle sacral artery, then the common iliac and inferior mesenteric arteries, and finally the aorta.

ANOMALIES IN NUMBER

Supernumerary Kidney

A supernumerary kidney is an uncommon anomaly, with less than 100 cases reported in the literature.[3,4] The embryologic basis shares some similarities with that found in ureteral duplication. There are either two ureteral buds arising from the mesonephric duct, leading to double ureters, or a branching of the ureteral bud, which results in a bifid collecting system. Either the two ureteral buds then join two separate metanephroi, or a splitting of the nephrogenic blastema occurs. This later develops into twin metanephroi after induction by the two ureteral buds.

The supernumerary kidney is caudal to the ipsilateral kidney in 60% of cases. A supernumerary kidney associated with complete ureteral duplication is more likely to be in a cranial location. There is generally one extra kidney, but as many as five separate renal masses have been reported. This anomaly occurs more frequently on the left side. The ureter of the anomalous kidney joins the ipsilateral ureter about as commonly as it enters the bladder separately, but only rarely is the ureter ectopic. The extra kidney has its own renal capsule and blood supply. The supernumerary kidney is often smaller, and one-third exhibit other pathologic changes (e.g., hydronephrosis and pyelonephritis). Renal function is frequently decreased in the smaller hypoplastic unit.

Most cases are diagnosed after the third decade of life. Presenting complaints are usually related to urinary obstruction or infection and include pain, fever, or an abdominal mass.[5] However, many patients remain asymptomatic throughout life, and 20% of reported cases were discovered at autopsy.[6] The diagnosis can be readily established via the use of nuclear renal scintigraphy, which will confirm the presence of functioning renal tissue.

Unilateral Renal Agenesis

Renal agenesis, whether unilateral or bilateral, results from a failure of the ureteral bud to induce the metanephric blastema. This could result from agenesis of the ureteral bud, failure of the bud to reach the blastema, absence or abnormality of the metanephric blastema, or failure of the ureteral bud to invade the metanephric blastema.[7] The etiology is most likely secondary to an abnormality with the ureteral bud, as opposed to the metanephric blastema, as the ipsilateral gonad—derived from adjacent mesenchymal tissue—is rarely affected. The high incidence of absent or malformed proximal Wolffian duct (WD) structures in the male and anomalies of the Müllerian duct (MD) structures in the female suggest that the embryologic insult affects the ureteral bud primarily in its early development.

It is unclear whether there is a genetic predisposition or if it is related to other prenatal factors. Parikh et al. found that diabetes and black maternal race were associated with an increased incidence of renal agenesis, but it is probably multifactorial, with both environmental and genetic factors playing a role.[8] A familial tendency has been reported, supporting the latter.[9] The reported incidence of this condition varies between series of patients collected from either clinical or autopsy data. Doroshow and Abeshouse estimated that unilateral renal agenesis (URA) is found in 1 of every 1100 autopsies.[10] The clinical incidence on imaging studies is 1 in 1500, suggesting that most cases are diagnosed during life.[11] Currently, most renal anomalies seen by pediatric urologists are detected prenatally, and URA is no exception, but fetal US studies have detected renal agenesis with a much lower frequency.[12,13] A number of patients previously reported with URA most likely had prior involution of multicystic or dysplastic kidneys. This has been documented to occur prenatally, and rapid involution of multicystic and dysplastic renal units has also been shown to occur early in postnatal life.[14–16] Hiraoka et al. have suggested that aplasia is the predominant cause of congenital solitary kidneys.[17] The presence of the splenic flexure of the colon in an orthotopic location would suggest the prior presence of a renal unit that has since involuted. There is a slight male predominance, and the condition occurs more frequently on the left side. This male predominance may reflect the earlier differentiation of the WD that takes place close to the time of ureteral bud formation. The ureteral bud is more likely to be influenced by abnormalities of the WD than those of the MD, which occurs later.

Associated Anomalies

The ipsilateral ureter is absent in approximately two-thirds of cases.[18] On cystoscopic examination, a hemitrigone will be present in patients with complete ureteral agenesis. This finding has been substantiated with cell lineage studies demonstrating that the trigone has a urogenital sinus origin and should form normally.[19] Anomalies of the contralateral ureter are common, with vesicoureteral reflux (VUR) the most frequent finding (~30%), followed by ureteropelvic (~11%) and ureterovesical (~7%) junction obstruction.[20–22] Although the ipsilateral adrenal gland may have a unique configuration, it is rarely absent (~8%) based on autopsy studies.[18] This is not surprising given the distinct embryological origins of the kidney and adrenal gland.

Genital anomalies, especially in the female, are much more frequently observed. Likewise, patients with known genital anomalies have an increased incidence of renal anomalies.[23] Regardless of sex, both gonads are usually normal. A variety of anomalies may result in the female from incomplete MD formation because of alterations in normal WD development. Approximately 30% of women with URA have an abnormality relating to WD development.[24] Most of the genital anomalies in female patients with URA are asymptomatic, but such anomalies often assume greater clinical importance, leading to earlier evaluation and diagnosis of the absent kidney. The most common problems involve the uterus and vagina. There is often a unicornuate or bicornuate uterus, and the ipsilateral horn and fallopian tube may be rudimentary or absent[25] (Figure 21.2). The fimbriated end of the fallopian tube, however, is usually fully formed and is analogous to the head of the epididymis in the male. A duplex uterus is attributable to a developmental anomaly of the urogenital septum, resulting in incomplete midline fusion of the MDs and a longitudinal vaginal septum. The development of the MD appears to be inhibited by the defective WD if the defect occurs early in development.[26] Defects of the ureteral bud that occur after MD fusion will affect only ureteral and renal development.[27] Obstruction of the lower genital tract can occur, leading to hydrocolpos or hematocolpos. In fact, Smith and Laufer have suggested the acronym OHVIRA to classify the syndrome of obstructed hemivagina and ipsilateral renal anomaly.[28] Patients present with a pelvic mass and/or pain and fail to menstruate at puberty.[29] Patients with complete Müllerian arrest will require vaginal construction to achieve adequate sexual function but will obviously be infertile. Complete absence or hypoplasia of the vagina, the Mayer–Rokitansky–Küster–Hauser syndrome, is frequently associated with agenesis of the kidney and occurs in approximately 1 in 5000 live female births.[30] This syndrome includes not only renal anomalies but also genital tract anomalies, ranging from upper vaginal atresia to total Müllerian agenesis in an otherwise phenotypically normal female with a normal 46,XX karyotype.

The testis and head of the epididymis, which are derived from the mesonephric tubules, are invariably present. All structures proximal to that point, which develop from the WD (the body and tail of the epididymis, vas deferens, seminal vesicle, ampulla, and ejaculatory duct), are absent in 50% of males with URA.[31] Conversely, in those patients presenting with an absent vas, the reported incidence of renal agenesis varies greatly. Donahue and Fauver found an absent kidney in 22/26 (85%) patients with an absent

vas deferens.[32] Goldstein and Schlossberg used computed tomography (CT) to evaluate 26 men with an absence of the vas deferens.[33] URA was noted in only four men, in all of whom the seminal vesicle was absent. Schlegel et al. found an 11% incidence of renal agenesis in infertile men with unilateral agenesis of the vas.[34] Nevertheless, in males the diagnosis of URA should be suspected during a physical examination when the vas deferens or body and tail of the epididymis are impalpable. This may be more common in adults undergoing evaluation for infertility. In infants and young boys, URA should be considered when vasal and/or epididymal anomalies are incidentally found at the time of orchiopexy.

Approximately 25%–40% of patients with URA have anomalies of other organ systems. The most frequently affected are the cardiovascular (30%), gastrointestinal (25%), and musculoskeletal (14%) systems.[35] URA is associated with several syndromes, including Turner's, Poland's,[36] Goldenhar's,[37] VACTERL association[38] and Klippel–Feil.[39]

Diagnosis and Imaging

There are no specific symptoms that suggest an absent kidney. Previously, most reports were compiled from autopsy series, but now prenatal screening is detecting URA. It has long been held that hypertrophy of the solitary kidney occurs as an adaptive compensatory response, and this has been demonstrated to occur in utero.[40] This is somewhat curious given the fact that the placenta is almost entirely responsible for filtration of blood and elimination of waste products during gestation. In any event, URA may be suspected by a number of radiological manifestations. US, radionuclide scintigraphy, and MRI have completely replaced arteriography in diagnosing URA. A plain film of the abdomen will often demonstrate that the gas pattern of the splenic or hepatic flexure of the colon is displaced into the renal fossa.[41,42] A retroperitoneal ultrasonogram with color Doppler will show the absence of the kidney and ipsilateral renal vessels. The diagnosis of URA can usually be confirmed with a dimercaptosuccinic acid (DMSA) scan showing absent uptake of the isotope on one side, with the contralateral kidney often showing compensatory hypertrophy.[43] A DMSA scan will also detect an ectopic (usually pelvic) or a crossed ectopic kidney in cases where the nonvisualized orthotopic kidney is thought to be absent.[44]

Historically, when a diagnosis of URA was confirmed, voiding cystourethrogram was recommended because of the nearly 30% incidence of contralateral reflux. Given the evolving paradigm in the diagnosis, treatment, and clinical significance of VUR, this once certain recommendation is somewhat debatable, especially in the absence of a contralateral renal anomaly on ultrasonographic and/or renal scintographic imaging. US and MRI are useful for examining the internal genital structures in females with a diagnosis of renal agenesis. In general, the uterus and cervix can be visualized in both infants and older girls. Renal sonography has been recommended for the screening of parents and siblings of children born with renal agenesis. Roodhooft et al. reported a 9% incidence of asymptomatic renal malformations in family members, with URA being the most common finding.[45]

Prognosis

There are both experimental and clinical studies suggesting that hyperfiltration of remnant nephrons may have an adverse effect on renal function, depending on the number of nephrons remaining.[46] There are reports of focal glomerulosclerosis, the renal lesion that develops in hyperfiltration, occurring in humans with URA.[47–49] Some studies have noted an increased rate of hypertension, proteinuria, and mild renal insufficiency.[50,51] However, others have noted normal renal reserve in patients with URA.[52]

There is fairly wide variability in terms of what constitutes a normal number of nephrons in humans. Consequently, it would follow that an individual with fewer functional nephrons would be at greater risk for renal insufficiency at any age, regardless of etiology. Moreover, contemporary evidence would suggest that subtle defects in ureteral bud branching can cause a reduced nephron number, which may lead to renal disease later in life.[53] Recently, Sanna-Cherchi et al. evaluated the long-term functional outcomes in individuals with CAKUT, including those with URA from a single pediatric nephrology center.[54] Somewhat surprisingly, patients with a solitary kidney had a 50% probability of requiring dialysis by 30 years of age. Notably, most of the patients with URA in this study were diagnosed during adolescence and had a normal creatinine level at the time of diagnosis. Interestingly, the patients diagnosed at birth had a slightly elevated creatinine level (0.68 mg/dL). These and other studies point out the fundamental differences in individuals with URA and adults who undergo unilateral nephrectomy. The number of nephrons in children with URA may be abnormally low, and those with fewer nephrons may be at greater risk for developing focal glomerulosclerosis.

From a practical standpoint, most parents will desire counseling on any dietary or activity restrictions for their child. The American Academy of Pediatrics recommends a "qualified yes" for participation by athletes with single kidneys in contact sports. In a recent study, Grinsell and colleagues reviewed data from the National Athletic Trainers' Association High School Injury Surveillance Study from 1995 to 1997.[55] Researchers analyzed data from more than 4.4 million "athlete exposures," defined as one athlete participating in one game or practice. Of 23,666 reported injuries, only 18 involved a kidney, and none of those were catastrophic or required surgery. The authors concluded that the data do not support limiting sports participation by athletes with otherwise normal single kidneys.

There is a paucity of evidence-based data to guide the management of patients with a single kidney who might be identified as at risk of progressive renal damage. A sensible approach to lifestyle factors that promote healthy living, such as avoiding obesity, smoking, and a high-salt diet, is essential, as they are likely to have adverse effects on renal hemodynamics and contribute to progression of chronic kidney disease (CKD)[56–58] in these nephron-deficient individuals. Additionally, it is known that obese individuals are more likely to develop proteinuria and CKD following unilateral nephrectomy.[59] Current suggestions for children with a normal-appearing single kidney include annual assessments of blood pressure and urinalysis for

proteinuria, the hallmarks of a progressive decrease in glomerular filtration rate.[60] Periodic laboratory evaluation of blood urea nitrogen and serum creatinine levels can be performed. Should there be hypertension, proteinuria, and/or impaired renal function, pediatric nephrology consultation should be obtained. The available options for attenuating the progression of CKD include dietary protein restriction,[61] control of proteinuria,[62] and optimum management of hypertension and hyperlipidemia, including therapy with angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers.[63]

Bilateral Renal Agenesis

Prior to the widespread use of prenatal US and the availability of legalized pregnancy termination in the United States, the incidence of bilateral renal agenesis (BRA) was about 1 in 4000 births with a male–female ratio of 2.5:1.[64] As stated previously, renal agenesis occurs when the ureteric bud fails to develop and thus fails to induce differentiation of the metanephric mesenchyme to renal tubular epithelium. In vitro models reveal that when the ureteric bud and metanephric mesenchyme meet, the ureteric bud branches and nephrons form within 3–7 days of culture; however, if they remain apart, nephrons do not form and the mesenchymal tissue undergoes apoptosis.[65]

BRA has been associated with a maternal body mass index of greater than 30 kg/m^2 prior to pregnancy (adjusted odds ratio [OR] = 1.92, 95% confidence interval [CI] 1.00–3.67), smoking during the periconceptional period (OR = 2.09, 95% CI 1.08–4.03), and binge drinking during the second month of pregnancy (OR = 3.64, 95% CI 1.19–11.1).[66] Advanced maternal age also appears to be a risk factor.[67]

Potter syndrome is a historical term that was used to define the typical appearance of a fetus or neonate exposed to severely decreased or absent amniotic fluid secondary to renal disease. Typically, this syndrome is characterized at birth by pulmonary hypoplasia, limb deformations (altered positioning of hands and feet, clubbed feet, and hip dislocation), and flattened facies. The most consistent finding is a prominent epicanthal fold that extends onto the cheek. The skin of these infants is very loose, particularly over the hands. It results from external compression of the fetus, limitation of fetal movement, and alteration in the dynamics of lung liquid movement due to severe oligohydramnios. Potter syndrome can also be seen in infants with normal kidneys with prolonged leakage of amniotic fluid or rarely with severe fetal growth restriction; thus, it is not pathognomonic of renal anomalies per se (Figure 21.3).

The diagnosis of BRA is based on sonographic nonvisualization of the fetal kidneys, ureters, and bladder, accompanied by oligohydramnios. The major nonspecific marker of BRA is severely reduced or absent amniotic fluid. In early pregnancy, the movement of fluid across the amnion, fetal membranes, and chorionic plate is thought to be the dominant source of amniotic fluid. Fetal urine becomes the main source after about 16 weeks of gestation. Therefore, amniotic fluid volume in pregnancies complicated by renal agenesis might appear normal in early pregnancy (i.e., prior to 16 weeks), even though sharply reduced or absent amniotic fluid volume is the most prominent ultrasonic feature of this disorder by the midtrimester.[68] The fetal kidneys and adrenal glands can be visualized by transabdominal US between the 12th and 15th weeks of gestation, with the prenatal detection rate for BRA reported to be between 84% and 91%.[69]

Interestingly, when siblings and parents of an index child with BRA were screened, 4.5% had URA, which is 1000-fold higher than the general population.[45,70] Recently, McPherson evaluated renal anomalies in families of individuals with congenital solitary kidneys that included renal agenesis or dysplasia or hypoplasia. The empiric risk was 7% for offspring, 4% for parents, and 2.5% for siblings. It was noted that this may be an underestimation, because not all relatives underwent US screening. The incidence of BRA in offspring of congenital solitary kidney probands was about 1%, which is significantly greater than the risk found in the general population but less than that for families with a history of BRA. This has led to the recommendation that for parents and siblings of infants born with either unilateral or BRA or dysgenesis, retroperitoneal US screening be performed to evaluate for renal anomalies.[45,71]

BRA is associated with other structural abnormalities in more than 50% of cases. The types of structural anomalies are similar to those in patients with congenital solitary kidney, although the frequency is lower. These abnormalities include a variety of syndromes associated with chromosomal anomalies, caudal dysgenesis, VACTERL (vertebral anomalies, anal atresia, cardiac defects, TE [tracheoesophageal] fistula, renal defects, limb defects), and isolated anomalies of the cardiovascular, skeletal, and central nervous systems.[71]

BRA is incompatible with extrauterine life because prolonged absence of amniotic fluid results in pulmonary hypoplasia, leading to severe respiratory insufficiency at birth. Fetuses are able to survive in utero since the placenta is responsible for fetal oxygenation and excretion of wastes; however, there is a higher rate of fetal loss that is probably related to cord compression. As many as 33% of fetuses with BRA die in utero, and approximately 40% of such infants are stillborn.[72] This poor prognosis has led to the recommendation of termination of the pregnancy if the diagnosis is made early in gestation.

ANOMALIES OF ROTATION

Abnormal rotation, or malrotation, is most commonly associated with an ectopic or fused kidney, but may also occur in kidneys that complete their ascent. As the normal maturing kidney assumes its final position in the renal fossa, it is oriented such that the calyces point laterally and the pelvis faces medially (Figure 21.1). The true incidence of this type of anomaly is probably understated because in many patients there are no clinical manifestations. Campbell reported only 17 cases of renal malrotation among 32,834 autopsies on adults.[73] Smith and Orkin found an incidence of 1 in 390 hospital admissions and stated that malrotation accounts for 10% of upper urinary tract anomalies.[74]

It is thought that medial rotation of the collecting system occurs simultaneously with renal migration. The

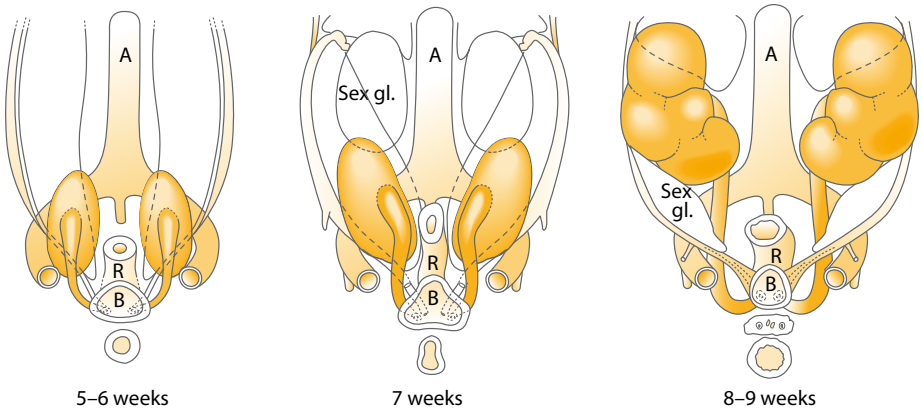

FIGURE 21.1 Ascent and rotation of kidneys during fetal life. The normal rotation of the kidney from facing forward to facing medially is shown. A, aorta; R, rectum; B, bladder; Sex gl, sex gland. (Adapted from Campbell MF. *Clinical Pediatric Urology*. Philadelphia: WB Saunders, 1951.)

kidney starts to turn during week 6, and it completes this process by rotating 90° toward the midline by the time ascent is complete at the end of the ninth week of gestation. The rotation of the fetal kidney has been proposed to be the result of differential growth, with more tubules being formed on the ventrolateral side than on the dorsomedial side.[75] This theory does not explain all the abnormalities of rotation. Weyrauch suggested that the ureteral bud makes more lateral contact with the renal blastema.[76] This may explain an anomalous initial position of the kidney, but does not explain normal renal rotation.

The different types of malrotation are depicted in Figure 21.4. The most common is an incomplete rotation, or nonrotation (Figure 21.5). The renal pelvis is anterior or between the fetal anterior and normal medial position in the adult. Other major types of anomalous rotation are reverse rotation and hyperrotation (excessive rotation), in which the kidney faces laterally, but these are rare (Figure 21.6). In reverse rotation, the renal pelvis rotates laterally and the renal vessels cross the kidney anteriorly to reach the hilum (Figure 21.7). In excessive rotation, the kidney rotates more than 180° but less than 360°. The pelvis faces laterally, but the renal vessels are carried posteriorly to the kidney. Less severe hyperrotation may leave the renal pelvis in a dorsal position. The renal blood supply does not appear to be the cause or a limiting factor in malrotation, but rather follows the course of renal nonrotation, hyperrotation, or reverse rotation.

Malrotation is usually discovered incidentally during imaging of the kidney. When symptoms occur, they are most often related to upper urinary tract obstruction and can be in the form of abdominal or flank pain, nausea, and/or emesis. Hematuria associated with hydronephrosis, infection, and calculus formation may also occur

FIGURE 21.2 Bicornuate uterus seen on hysterosalpingogram with filling of both fallopian tubes. The vagina was normal in this patient with an absent right kidney.

FIGURE 21.3 Potter's facies. (Courtesy of Dr. Catherine Poole, University of Miami, Florida.)

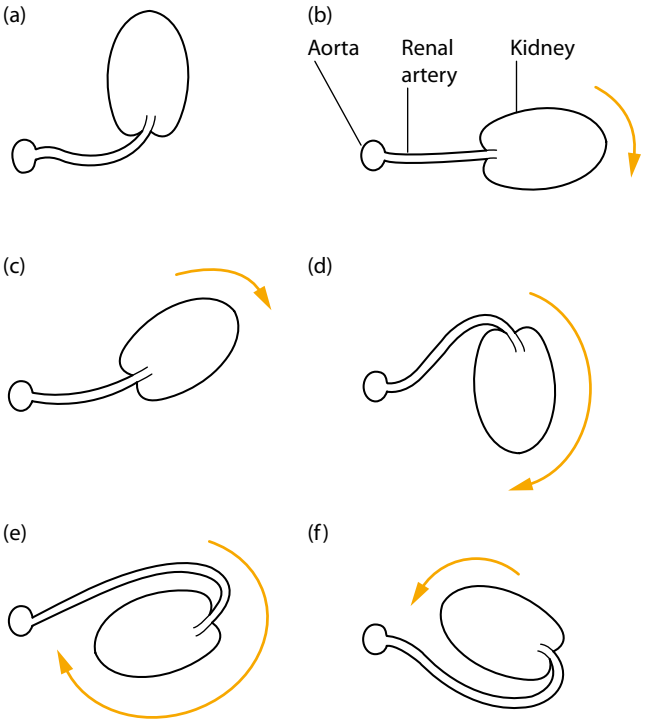

FIGURE 21.4 Rotation of the kidney during its ascent from the pelvis. The left kidney (with its renal artery) and the aorta are viewed in transverse section to show normal and abnormal rotation during its ascent to the adult site. (a) Primitive embryonic position, hilus faces ventrad (anterior). (b) Normal adult position, hilus faces mediad. (c) Incomplete rotation. (d) Hyper-rotation, hilus faces dorsad (posterior). (e) Hyper-rotation, hilus faces laterad. (f) Reverse rotation, hilus faces laterad. (Adapted from Parrott TS, Shandalakis JE, Gray SW. The kidney and ureter. In: Shandalakis JE, Gray SW, eds. Embryology for Surgeons. *The Embryological Basis for the Treatment of Congenital Anomalies*, 2nd edn. Baltimore: Williams and Wilkins, 1994: 594–670.)

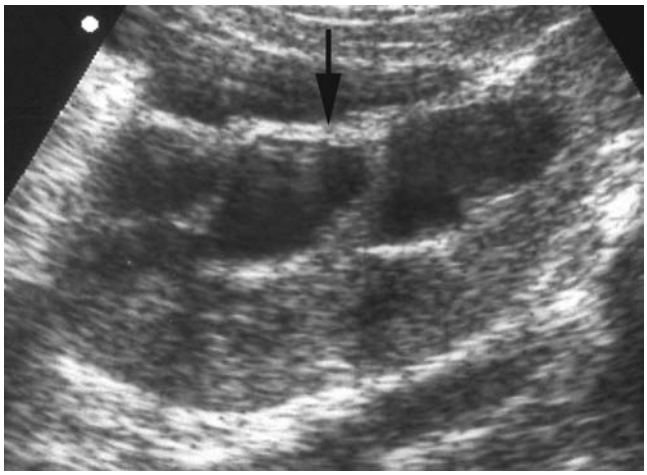

FIGURE 21.5 Ultrasound demonstrating malrotation of the right kidney. This results in an anterior location of the renal collecting structures (arrow) on ultrasound, rather than the usual posteromedial orientation.

FIGURE 21.6 CT demonstrating excessive rotation of the right kidney.

secondary to poor urinary drainage. Obstruction may be secondary to compression of the ureter from an anomalous accessory vessel or other obstructive lesions that also occur in normally rotated kidneys (e.g., calculus). The calices are often distorted, even without any associated obstruction. Axial imaging, such as CT or MRI, can be very informative. The upper third of the ureter may be displaced laterally and the renal pelvis may appear elongated, suggesting obstruction or effacement by an extrinsic mass. Treatment of malrotation is reserved for alleviation of associated obstruction, calculi, or infection secondary to poor drainage.

ANOMALIES OF ASCENT

Renal ectopia (Greek: *ek* ["out"] and *topos* ["place"]) is the term used to describe a kidney that lies outside the renal fossa. The kidney migrates cephalad early in gestation to reach its normal position. Failure of ascent can be due to a number of factors: abnormality of the ureteral bud or metanephric blastema, genetic abnormalities, teratogenic causes, or anomalous vasculature acting as a

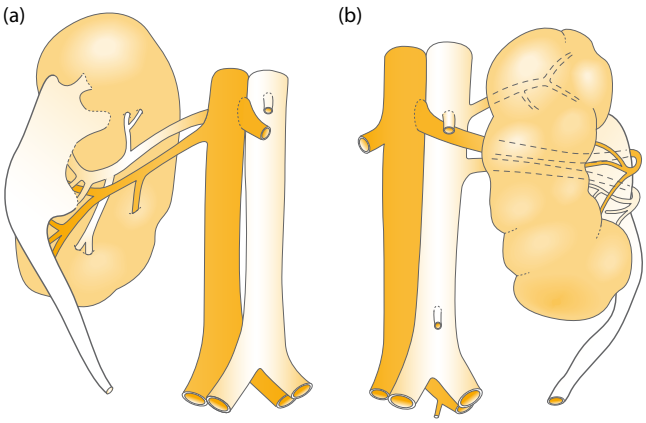

FIGURE 21.7 Abnormal renal rotation: (a) reverse rotation; (b) hyper-rotation. (Adapted from Weyrauch HM Jr. *Surg Gynecol Obstet* 1939;69:183–99.)

barrier to ascent.[77] During ascent, the kidney receives its blood supply from the middle sacral artery, iliac artery, and finally, the aorta. The anomalous blood supply that is invariably present is dependent on the final position of the kidney and is not believed to be the cause of the malposition. However, the blood vessels are frequently short, rendering surgical mobilization very difficult.

Incidence

The incidence of renal ectopia in postmortem studies varies from 1 in 500 to 1 in 1290.[78,79] The incidence is historically higher in autopsy series than in clinical studies, suggesting that many cases remain unrecognized throughout life.[77] With increasing clinical detection, however, the incidence among hospitalized patients has approached the autopsy rate of about 1 in 900.[80] There is a slight predilection for the left side, and 10% of cases are bilateral. Simple renal ectopia refers to a kidney that remains in the ipsilateral retroperitoneal space. This is in contradistinction to renal ptosis, in which the kidney initially is located in its proper place (and has normal vascularity) but moves downward in relation to body position. The differentiation between a ptotic kidney and renal ectopia can be difficult, but there are several discerning features. The length of the ureter may be helpful. In renal ectopia, ureteral length corresponds to the location of the kidney; in a ptotic kidney, the ureter appears redundant. The ptotic kidney is mobile and usually can be manipulated into its normal position. The most common position for simple ectopia is in the pelvis (sacral or pelvic kidney) opposite the sacrum or below the aortic bifurcation.[79] The lumbar or iliac ectopic kidney is one that is fixed above the crest of the ileum but below the level of L-2 and L-3. Other positions are abdominal, thoracic, and crossed. Crossed renal ectopia refers to a kidney positioned contralateral to the side in which its ureter inserts into the bladder (see discussion on anomalies of fusion later in this chapter). Lastly, malrotation often accompanies renal ectopia (Figure 21.8).

FIGURE 21.8 Malrotated ectopic kidney opposite lower lumbar vertebrae.

Diagnosis

With the increasing use of various imaging modalities, the incidence of an asymptomatic ectopic kidney is increasing. The infrequent cases of symptomatic renal ectopia diagnosed in childhood present with symptoms attributed to the genitourinary or gastrointestinal system, such as vague abdominal pain or renal colic secondary to ureteral obstruction (e.g., ureteropelvic junction [UPJ] obstruction or urolithiasis). The abnormal position of the kidney results in a pattern of direct and referred pain that is atypical for colic and may be misdiagnosed as acute appendicitis or as pelvic inflammatory disease in female patients. Urinary tract infection is the presentation in about 30% of children. The ectopic kidney may also be noted incidentally, most frequently on prenatal US. A pelvic kidney is the most common finding in a fetus with an empty renal fossa and normal amniotic fluid volume.[81]

Historically, pelvic kidneys were often difficult to recognize on excretory urography because they overlie the bony pelvis, which obscures the collecting system and can lead to a misdiagnosis (Figure 21.9). However, most can be now be identified by US or radionuclide imaging.[82] Whenever a kidney is absent on US, radionuclide imaging is indicated to exclude an ectopic kidney. However, if the kidney is totally nonfunctional, a CT scan or MRI may be the best method of localization.[83] If cystoscopy is performed, the ureteral orifices are invariably normal (unless the ureteral orifice is also ectopic). If surgery is indicated on an ectopic kidney, retrograde pyelography can be used to delineate the collecting system anatomy (Figure 21.10). Magnetic resonance arteriography can also be performed preoperatively to define the anatomy of the renal vasculature, which is especially important in cases of solitary ectopia.

Hydronephrosis is frequently noted in ectopic kidneys. Gleason et al. found that half of the dilatation could be attributed to UPJ or ureterovesical junction (UVJ) obstruction.[84] Obstruction in the ectopic kidney is frequently due to a high insertion of the ureter on the renal pelvis (Figure 21.11). High-grade reflux was responsible for 26% of hydronephrotic kidneys, and the extrarenal collecting system with malrotation accounted for the remainder. Diuretic renography may be helpful to distinguish these abnormal pyelocaliceal patterns from UPJ obstruction. The ectopic kidney can be clearly shown on the renal scan, but the gamma camera should be placed anteriorly to obtain better images (Figure 21.12).

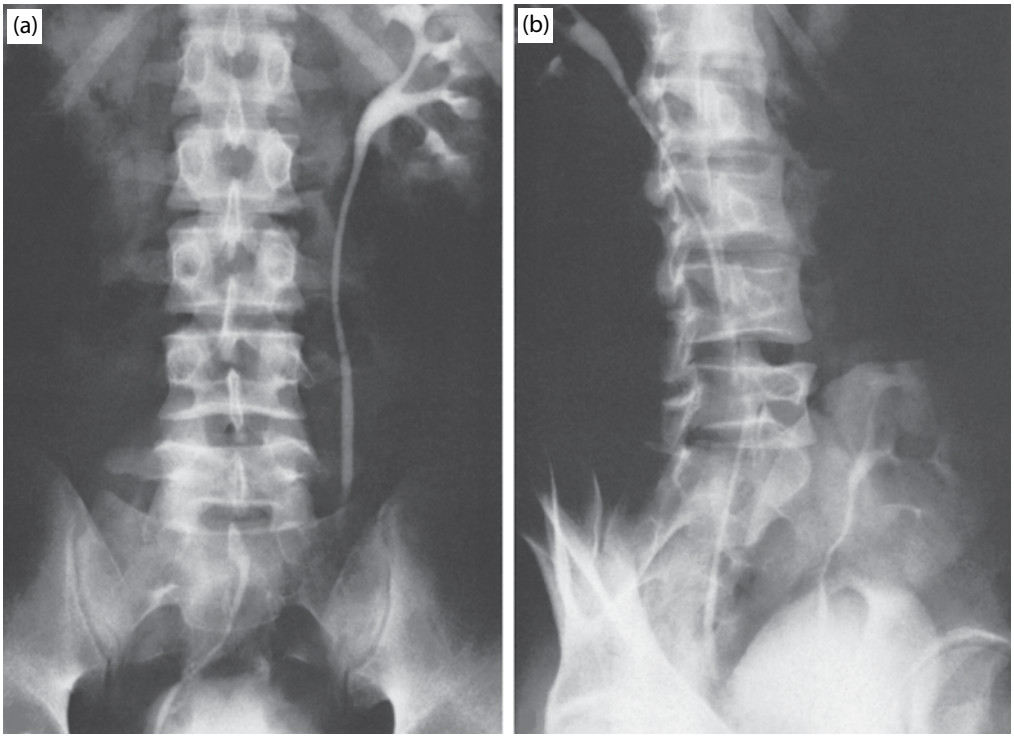

FIGURE 21.9 Excretory urogram in patient with a right pelvic kidney. (a) The short right ureter is seen overlying the bony structures. (b) Oblique film allows much better visualization of the collecting system and renal outline.

Associated anomalies

The contralateral kidney is abnormal in up to one-half of patients.[77] There is a 10% incidence of contralateral renal agenesis. Associated VUR is found in 70%–85% of children with an ectopic kidney.[85] The adrenal gland is invariably orthotopic. Genital anomalies are common, with an incidence ranging from 10% in males to 75% in females.[86] In males, the most common abnormalities are hypospadias and undescended testes.[85] Anomalies of the reproductive organs in the female include duplication of the vagina, bicornuate uterus and hypoplasia or agenesis of the uterus or vagina.[87,88] These may become clinically important during pregnancy and may require cesarean section.[86] Anomalies of other organ systems also occur with increased frequency. Skeletal anomalies are present in up to 50% of children. The most common include asymmetry of the skull, rib abnormalities, dysplastic vertebrae, and absent bones. Cardiovascular lesions were noted in 9 of the 21 children, and gastrointestinal abnormalities were found in one-third of patients in one study.[77] Others, however, have reported a lower incidence of associated extragenitourinary anomalies.[86]

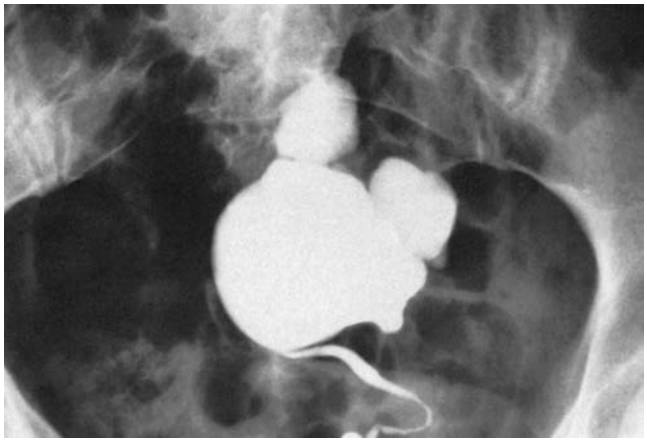

FIGURE 21.10 Retrograde pyelogram in a patient with a symptomatic ureteropelvic junction obstruction in a left pelvic kidney.

Management

Overall, renal disease will develop in 40% of patients with a solitary pelvic kidney, with the most common problem being a UPJ obstruction.[84,86] This may be due to the malrotation and high ureteral insertion, or an anomalous vessel that partially obstructs the collecting system. Obviously, treatment must be individualized. Most cases have traditionally been managed via a transabdominal approach for pyeloplasty; however, laparoscopy is increasingly being utilized in these cases.[89,90] The goal of surgery is to achieve dependent drainage, and in some cases, ureterocalicostomy may be best. Endopyelotomy has been used in a small number of selected patients with reasonable success.[91] Renal stones may develop in these kidneys from either infections or sluggish drainage (Figure 21.13). Historically, these were managed with open removal, but contemporary literature would suggest that pyelolithotomy is amenable to a laparoscopic approach.[92] Minimally invasive endourologic techniques, such as percutaneous

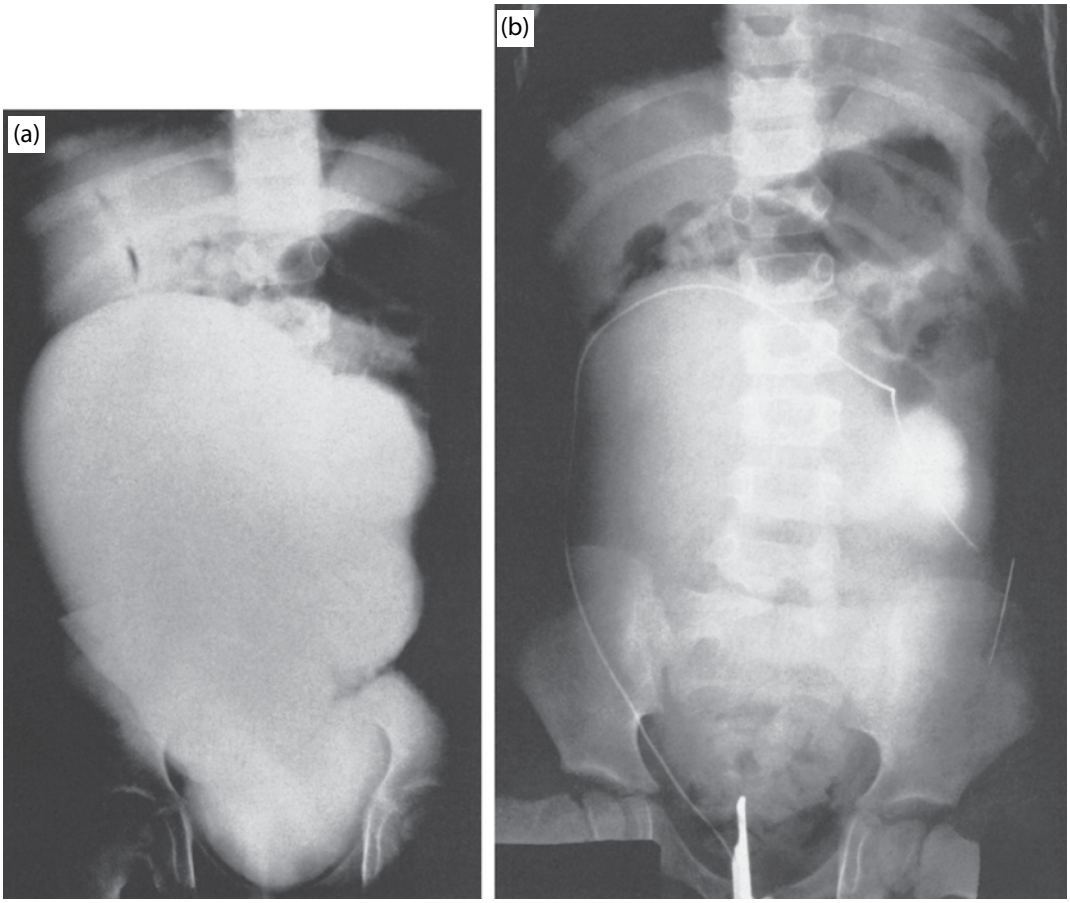

FIGURE 21.11 Ectopic solitary pelvic kidney in a 6-year-old boy with gross hematuria. (a) Excretory urogram showing giant hydronephrosis. (b) Retrograde pyelogram showing a catheter in the ureter with high insertion into pelvis.

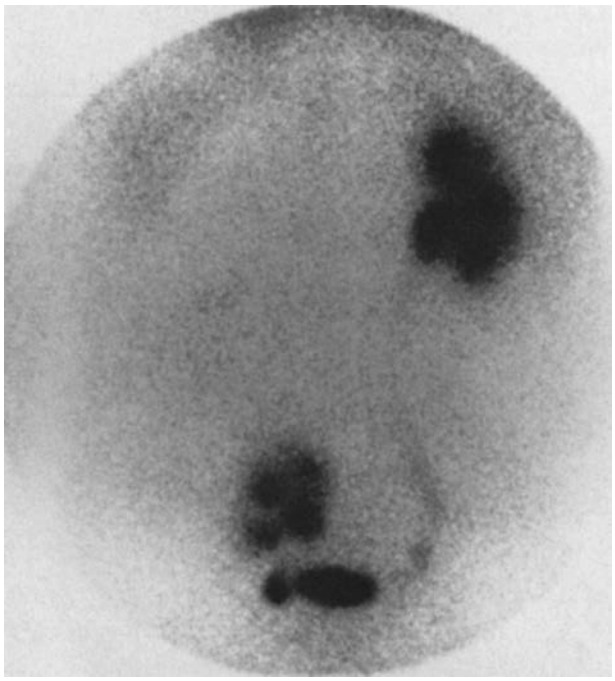

FIGURE 21.12 Renal scintigram of a right pelvic kidney. The camera was placed anteriorly in this patient with bilateral pyelocaliectasis.

nephrolithotomy, extracorporeal shock wave lithotripsy, and ureteroscopy, can also be utilized, particularly if the ureter is dependent in position. An important consideration in management is that the contralateral kidney is commonly abnormal, so that every effort should be made to preserve renal parenchyma.

Thoracic Kidney

The rarest form of renal ectopia exists when the kidney is positioned considerably higher than normal. Excessive cranial migration of the kidney results in a thoracic kidney. N'Guessan et al. prefer to call this a "superior ectopic kidney" because most high kidneys actually lie below the diaphragm.[93] Intrathoracic ectopia denotes either a partial or a complete protrusion of the kidney above the level of the diaphragm into the posterior mediastinum. This accounts for less than 5% of cases, with an incidence of 1 in 13,000 autopsies, with more than 140 cases reported.[78,94] The left side is more commonly involved, and there is a male predominance. The condition is rarely bilateral.[93]

Renal ascent is normally complete by the eighth week of gestation. An intrathoracic kidney may be the result of accelerated ascent prior to diaphragmatic closure or delayed closure of the diaphragmatic anlage, allowing continued ascent.[93] The renal vascular supply often arises from the normal site of origin on the aorta, but may arise more

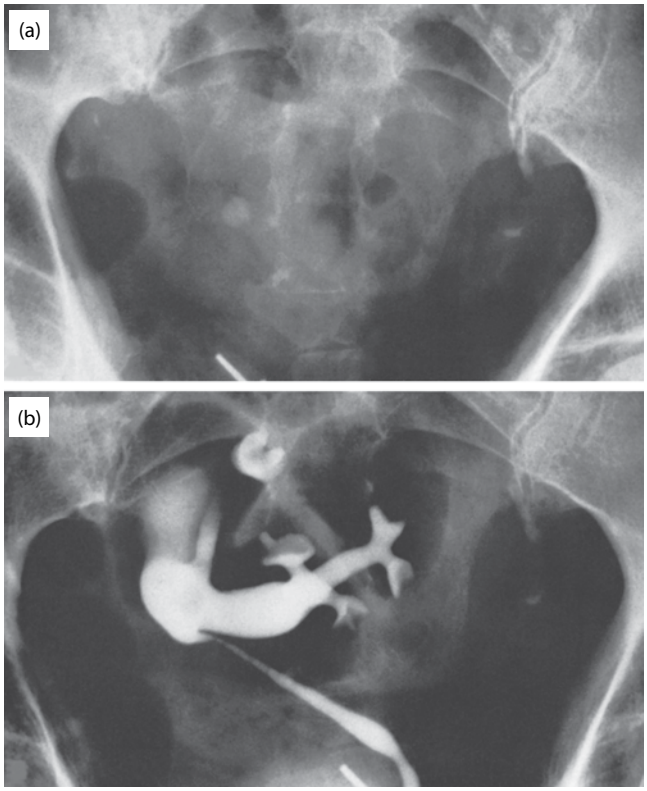

FIGURE 21.13 Left pelvic kidney. (a) Kidney–ureter–bladder (KUB) study revealed opaque calculus in the true pelvis. (b) Retrograde pyelogram confirmed the stone to be within the renal pelvis of the pelvic kidney.

superiorly.[95] The ureter and hilar vessels enter through the foramen of Bochdalek. The adrenal gland frequently remains caudal to the kidney in its normal location.[93] A superior ectopic kidney in association with a Bochdalek's hernia is uncommon. In this circumstance, there is herniation of other viscera through the diaphragm, and the kidney is mobile and can be easily withdrawn from the thorax. The kidney otherwise appears normal and has generally completed rotation.

In general, the thoracic kidneys function normally and most patients are asymptomatic. As with most renal anomalies, prenatal diagnosis is possible and UPJ obstruction has been noted and treated successfully.[94] The condition is most often detected on routine chest radiographs as a suspected mediastinal mass. Contrast-enhanced axial imaging (i.e., CT or MRI) can aid in confirming the diagnosis.

ANOMALIES OF FUSION

The congenital renal anomaly that produces some of the most bizarre-looking and perhaps most interesting urograms is the result of fusion of two or more kidney masses. Because the mechanisms responsible for normal complete ascent of the kidney during gestation are not entirely known, the cause of crossed ectopia and/or fusion remains elusive. There are several proposed mechanisms. The kidneys cross the umbilical arteries as they ascend out of the pelvis. Wilmer suggested that crossover occurs as a result of pressure from abnormally placed umbilical arteries that prevent cephalad migration of the renal unit, which then follows the path of least resistance to the opposite side.[96] Malposition of the umbilical arteries may also cause the developing nephrogenic blastemae to fuse in the midline, resulting in a horseshoe kidney. Alexander et al. theorized that crossed ectopia is a ureteral phenomenon, with the developing ureteric bud wandering to the opposite side and inducing differentiation of the contralateral nephrogenic anlage.[97] Cook and Stephens postulated that crossover is the result of malalignment and abnormal rotation of the caudal end of the developing fetus.[98] Fusion of the metanephric masses may occur when the renal anlagen are still in the true pelvis before or at the start of cephalad migration, or it may occur during the latter stages of ascent. The extent of fusion is determined by the proximity of the developing renal anlagen to one another. After fusion, advancement of the kidneys toward their normal location is impeded by midline retroperitoneal structures (e.g., aortic bifurcation, inferior mesenteric artery, and base of the small bowel mesentery) and malrotation is present in all cases.[99,100] Teratogenic factors and genetics have also been implicated.[101,102]

Horseshoe Kidney

The horseshoe kidney is the most common renal fusion anomaly, with the two renal units joined at their lower poles in more than 90% of cases (Figure 21.14). The isthmus crossing the midline joining the two kidneys consists of either renal parenchyma or fibrous tissue. The horseshoe kidney is usually positioned low in the abdomen, with the isthmus lying just below the junction of the inferior mesenteric artery and aorta. It is postulated that the inferior mesenteric artery obstructs the isthmus and prevents further ascent. Although usually situated anterior to the great vessels, the isthmus may cross posterior to the aorta and/or inferior vena cava.[103]

The reported incidence of horseshoe kidney is approximately 1 in 400, with contemporary radiologic literature quoting an incidence of 1 in 666 individuals.[78,104] The abnormality is more common in males. In autopsy series, this anomaly is found more commonly in children, which is attributed to the high incidence of associated congenital anomalies responsible for their untimely demise.[105] This is in comparison with the 3.5% incidence of associated congenital malformations in adults discovered to have horseshoe kidneys. Horseshoe kidneys have been reported in identical twins and in several siblings within the same family.[106]

Diagnosis

Clinical features from an affected horseshoe kidney are often vague and nonspecific. In the absence of a palpable mass or clinical symptomatology, the anomaly is not suspected until an imaging study is obtained. Prenatal US is now detecting most horseshoe kidneys.[81] The classic features of a horseshoe kidney have been noted on excretory

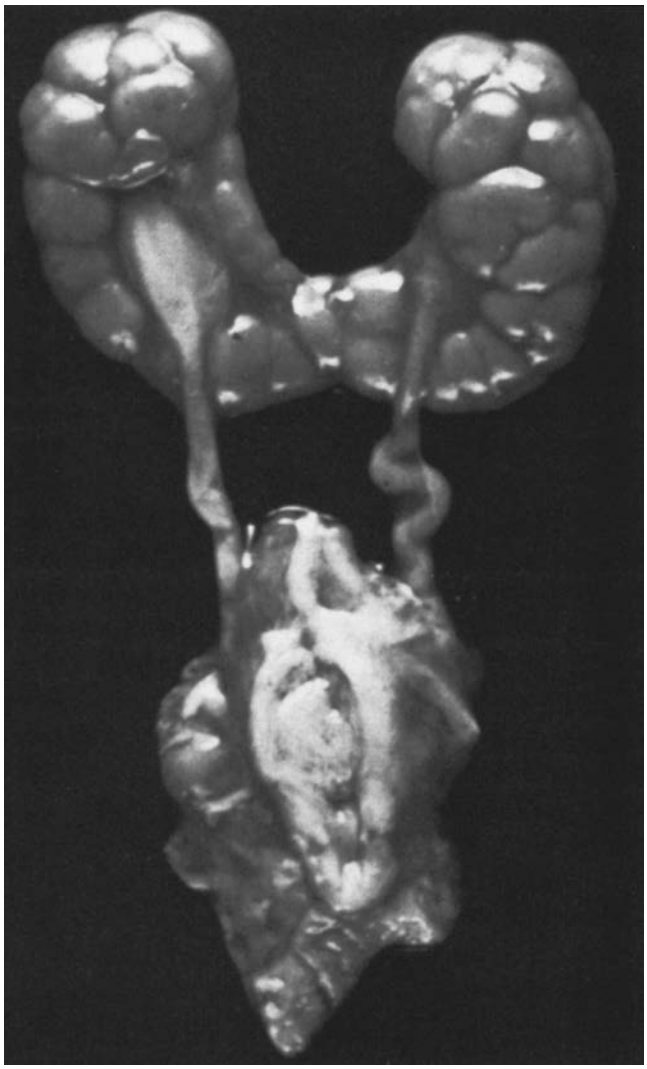

FIGURE 21.14 Horseshoe kidney, postmortem specimen

urography, which is now seldom performed in children (Figure 21.15). Malrotation of the kidney is always present and is attributed to very early fusion of the kidneys before rotation is complete. The renal pelves remain anterior, with the ureters crossing the isthmus. The orientation of the calices is generally anteroposterior, but the lowermost calices invariably point toward the midline, medial to the ureter. The course of the ureters is variable, but they often lie anterior to the pelvis. Other pertinent urographic findings are low-lying kidneys, and the lower outer border of the kidney appears to continue across the midline. The diagnosis of a horseshoe kidney can be confirmed by a variety of imaging techniques, including US, CT, and MRI (Figure 21.16). In general, the fusion of the kidneys can be clearly visualized with any of these studies (Figures 21.17 and 21.18). Previously, renal arteriography was often performed before surgery to delineate the vasculature. In the majority of cases, there are multiple renal vessels. The blood supply to the isthmus is particularly variable and often supplied by a separate vessel. This may arise from the aorta, common iliac, or inferior mesenteric arteries.

FIGURE 21.15 Typical appearance of horseshoe kidney on an excretory urogram.

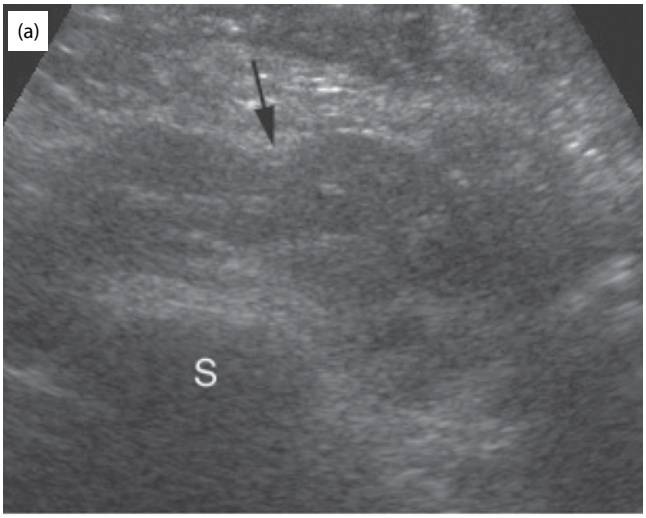

FIGURE 21.16 Horseshoe kidney. (a) Ultrasound demonstrates the isthmus (arrow), which is only partially visible anterior to the spine (S). (b) CT of the same patient better demonstrates the fused lower poles (arrows).

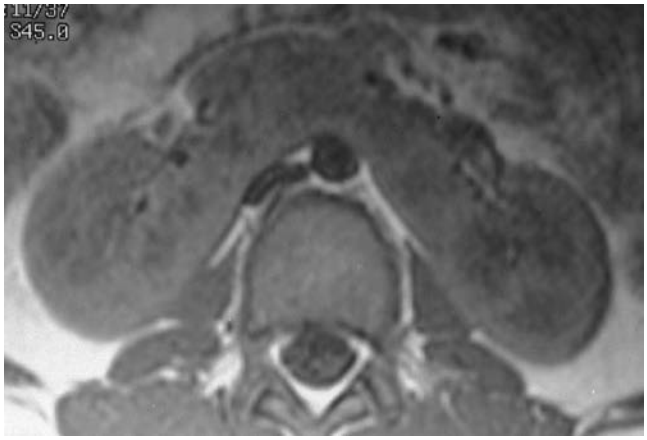

FIGURE 21.17 MRI of a patient with horseshoe kidney.

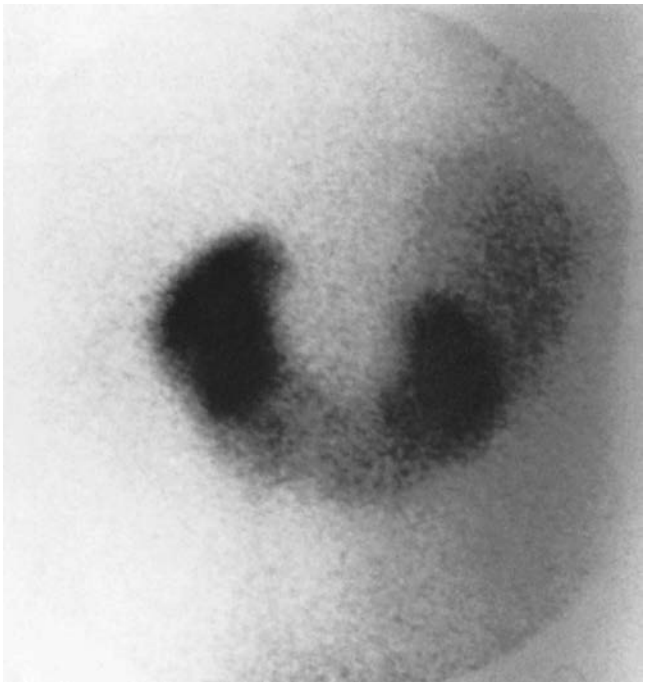

FIGURE 21.18 Renal scan in a patient with horseshoe kidney showing minimal function of the isthmus.

Associated Anomalies

There is a frequent association of other anomalies in children with horseshoe kidney, especially when the horseshoe kidney is discovered in the newborn period. Zondek and Zondek examined the postmortem records of 99 individuals with horseshoe kidneys.[107] Infants who were stillborn or who died within the first year of life had a 78% incidence of other malformations. This implies that a horseshoe kidney occurs more often in association with other serious congenital anomalies. The most commonly affected organ systems were the gastrointestinal, skeletal, cardiovascular, and central nervous systems. Boatman et al. reported that one-third of patients with horseshoe kidney had at least one other abnormality.[108]

Several well-known syndromes have a predisposition for horseshoe kidneys. Trisomy 18 is associated with a 21% incidence of renal fusion.[109] More than 60% of patients with Turner's syndrome have renal abnormalities, including horseshoe kidney, ureteral duplication, or other minor abnormalities.[110] One study noted a 15% prevalence of horseshoe kidney in females with Turner's syndrome.[111] There is also an increased incidence of horseshoe kidney in patients with neural tube defects.[112] Other genitourinary abnormalities are also encountered with increased frequency, including 10% of patients who have ureteral duplication, and up to 80% of children who undergo evaluation are found to have VUR.[113] A more recent report by Cascio et al. found VUR in 13/40 patients with horseshoe kidney undergoing cystography.[114] Multicystic dysplasia[115] and autosomal dominant polycystic kidney disease have also been reported.[116] Hypospadias and undescended testes occur in 4% of the males, and bicornuate uterus or septate vagina in 7% of females.[108] Retrocaval ureter has been found in association with a horseshoe kidney in six patients.[117]

Prognosis

A horseshoe kidney, in and of itself, is not thought to affect life expectancy. Nearly one-third of patients with a horseshoe kidney remain undiagnosed throughout life.[116] In fact, Glenn observed patients with horseshoe kidneys for an average of 10 years after discovery and found that almost 60% of these remained asymptomatic.[118] Only 13% had persistent urinary infection or pain, and 17% developed recurrent calculi. Most women are able to progress through pregnancy and delivery without adverse effects because a horseshoe kidney is located above the pelvic inlet.[119] In those patients with problems, symptoms are most often secondary to hydronephrosis, UTI, or urolithiasis. These patients generally present with vague abdominal pain. Patients can develop abdominal pain and nausea, with hyperextension of the spine (Rovsing syndrome), presumably resulting from stretching of the isthmus. Operations to divide the isthmus were once performed to relieve pain, but this procedure has largely been abandoned, as it has been demonstrated to have little merit.[116,118]

UPJ obstruction is the most common cause of hydronephrosis, occurring in approximately one-third of patients diagnosed in their lifetime. Kao et al. performed diuretic renography in 22 children with a horseshoe kidney detected on routine screening.[120] Only 1 of 44 renal units (2.3%) was found to have obstructive hydronephrosis. This suggests that most cases of obstruction are acquired over time, by either a high ureteral insertion or an anomalous renal vessel. It must be recognized that the calices may have an abnormal appearance as a result of the malrotation alone, and that not all these kidneys are obstructed. Kao et al. showed that 25% of renal units had some stasis prior to administration of diuretic.[120] In some children, the upper urinary tract dilatation may be secondary to VUR (Figure 21.19).

The increased risk of urolithiasis is attributed to stasis secondary to hydronephrosis, but metabolic factors should not be overlooked.[121] A recent multicenter study showed that all patients with a horseshoe kidney and calculi had some metabolic abnormality.[122] Hypercalcuria,

FIGURE 21.19 Horseshoe kidney. Voiding cystourethrogram demonstrating high-grade vesicoureteral reflux into the left renal moiety. Note the medial pointing calyx in the lower pole extending into the isthmus.

hypocitraturia, and low urine volumes were the most common defects. When stone disease is present, extracorporeal shock wave lithotripsy, ureteroscopy, and percutaneous nephrolithotomy yield comparable stone-free rates of between 70% and 80%, depending on the definition of success and number of procedures (including ancillary procedures) required to achieve stone-free status.[123–125]

More than 100 cases of renal malignancy have been reported in patients with a horseshoe kidney, with a number of tumors arising from the isthmus.[126,127] There appears to be an increased incidence of renal pelvic tumors and nephroblastoma in patients with horseshoe kidneys compared with the general population.[127,128] It has been suggested that the increased occurrence of chronic infection, obstruction, and stone formation may contribute to the higher than expected incidence of renal pelvic tumors. Renal cell carcinoma accounts for about half of the kidney cancer cases, although the incidence is no greater than that in the general population. Interestingly, Wilms' tumor is the second most common tumor found in horseshoe kidneys. In a review of National Wilms Tumor Study Group (NWTSG) patients, Mesrobian et al. found that there was a sevenfold increased risk of a Wilms' tumor developing in patients with a horseshoe kidney.[129] Neville et al. subsequently updated the NWTSG experience and identified 41 children with Wilms' tumor arising in a horseshoe kidney.[130] Most of these tumors were found on the left side, rarely in the isthmus, and practically all had favorable histology.

FIGURE 21.20 Crossed ectopia, with the right kidney crossing midline and fused to the lower pole of the left kidney.

Crossed Renal Ectopia

Crossed renal ectopia is the second most common fusion anomaly. As stated previously, the mechanisms responsible for renal ascent are not well defined, and therefore the exact cause of crossed renal ectopia remains largely unknown. The ectopic kidney crosses the midline to lie on the opposite side from its ureteral insertion into the bladder (Figure 21.20). The four varieties of crossed renal ectopia are illustrated in Figure 21.21. The incidence of crossed ectopia has been placed at 1 in 7000 autopsies.[80] Crossed renal ectopia with fusion is the most common type and accounts for 85% of the cases. Crossed ectopia without fusion represents fewer than 10% of all cases, and solitary crossed ectopia and bilateral crossed ectopia are exceedingly rare.[131] With all these abnormalities, there is a slight male predominance, and crossing from left to right occurs more frequently than right to left.

McDonald and McClellan described six different varieties of crossed ectopia with fusion (Figure 21.22).[132] The most common form is unilateral fused type with inferior ectopia, in which the upper pole of the crossed kidney is fused to the lower pole of the normally positioned kidney. The renal pelves remain in their anterior position, representing a failure to complete medial

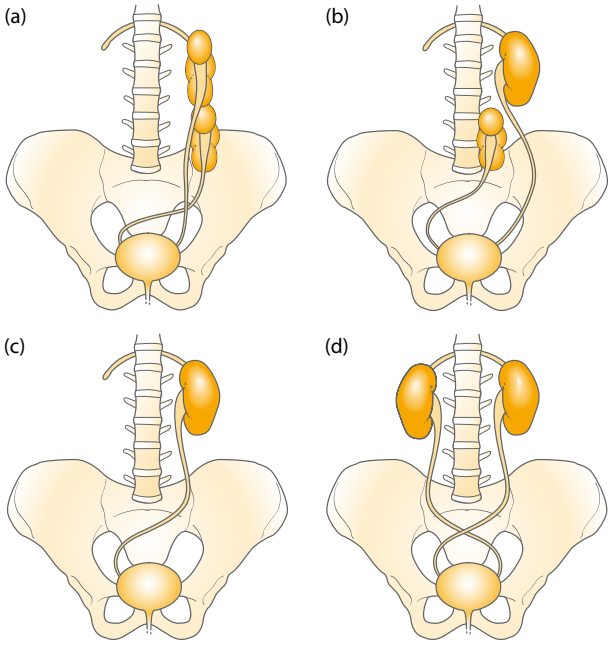

FIGURE 21.21 Four varieties of crossed renal ectopia: (a) with fusion; (b) without fusion; (c) solitary; and (d) bilateral. (Redrawn from McDonald JH, McClellan DS. *Am J Surg* 1957;93:995–1002; as reproduced by Abeshouse BS, Bhisitkul I. *Urol Int* 1959;9:63–91.)

rotation. The second most common type is the sigmoid, or S-shaped, kidney. The crossed kidney is inferior, but both kidneys have completed their rotation so that the two renal pelves face in opposite directions. The fusion of the two kidneys probably occurs later, after axial rotation is completed.

The other four types of fusion are much less common. The lump, or "cake," kidney and the "disk" kidney both involve extensive fusion of the two renal masses. In an L-shaped kidney, the crossed kidney assumes a transverse position. The least common type is the superior ectopic kidney, in which the crossed ectopic kidney lies superior to the normal kidney. The two kidneys may also fuse side to side and ascend together to the renal fossa (Figure 21.23).

Diagnosis

Historically, excretory urography identified most cases of crossed renal ectopia, but currently, US and DMSA radionuclide renal scans have revealed more asymptomatic cases.[44] The vascular supply to these kidneys is quite variable.

Renal arteriography often demonstrates multiple anomalous branches to both kidneys arising from the aorta, or common iliac artery. Rarely will the renal artery cross the midline to supply the crossed kidney.[133]

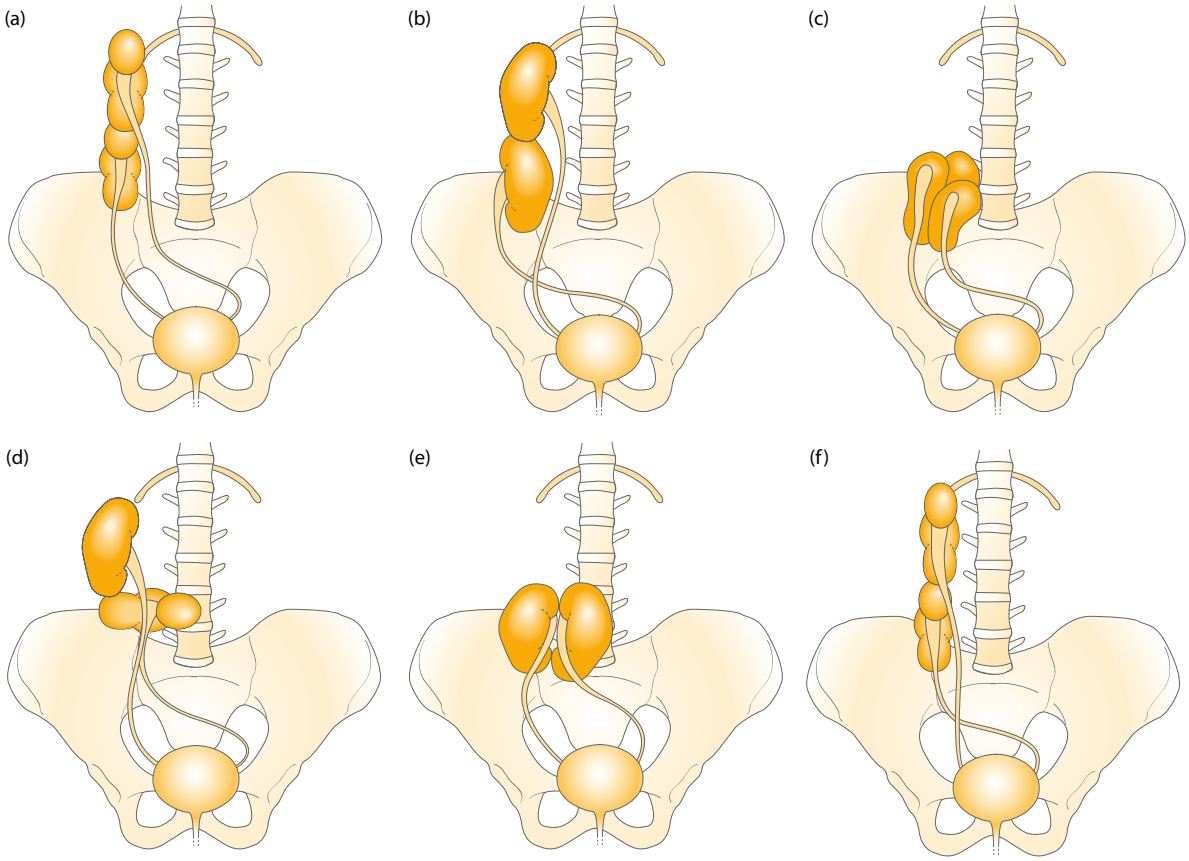

FIGURE 21.22 Six varieties of crossed renal ectopia with fusion: (a) unilateral fused kidney, superior ectopia; (b) sigmoid or S-shaped kidney; (c) 'lump' kidney; (d) L-shaped kidney; (e) 'disk' kidney; and (f) unilateral fused kidney, inferior ectopia. (Redrawn from McDonald JH, McClellan DS. *Am J Surg* 1957;93:995–1002; as reproduced by Abeshouse BS, Bhisitkul I. *Urol Int* 1959;9:63–91.)

FIGURE 21.23 Crossed fused ectopia. Intravenous pyelogram of a child with crossed ectopia, without obstruction.

Associated Anomalies

There is an increased incidence of other malformations, including orthopedic or skeletal anomalies, imperforate anus, and septal cardiac defects.[80] The highest incidence of associated anomalies occurs in children with solitary renal ectopia and involves both the skeletal system and genital organs.[84] This is most likely related more to renal agenesis than to the ectopic anomaly per se (see the "Unilateral Renal Agenesis" section). Fifty and forty percent of solitary crossed renal ectopia have a skeletal or genital abnormality, respectively.[134] The most common genital abnormalities in males are cryptorchidism and the absence of the vas deferens; in the female, it is vaginal atresia or a unilateral uterine abnormality.[131]

The ureter in the crossed ectopic kidney usually enters the bladder, and its orifice is only rarely ectopic.[80] The most commonly associated abnormality is VUR, which is frequently noted in the ectopic kidney.[85] Less common problems include UPJ obstruction, renal dysplasia, and renal tumors.[135]

Prognosis

Most patients with crossed renal ectopia have normal longevity and are discovered incidentally, often by antenatal sonography when two kidneys are not identified.[81] When symptoms do occur, they are often related to infection and obstruction. Abeshouse and Bhisitkul[80] reported that one-third of patients had pyelonephritis and one-quarter had hydronephrosis (Figure 21.24). The caliceal dilatation

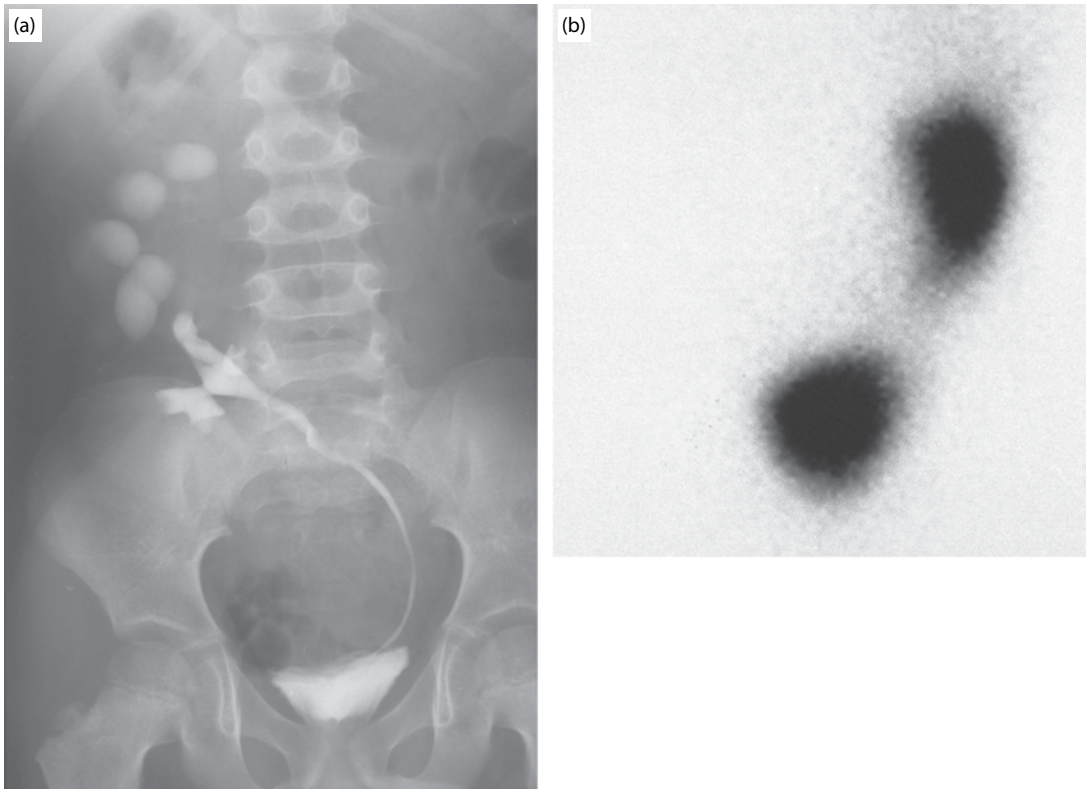

FIGURE 21.24 Crossed fused ectopia. (a) The left kidney crosses the midline. The presence of fusion is difficult to ascertain with confidence on this intravenous pyelogram. Obstruction is noted in the normally positioned right kidney. (b) 99mTc MAG3 radioisotope scan shows increased tracer activity in the right abdomen only.

and distortion may be secondary to the malrotation or the presence of VUR. Urolithiasis has been found in up to one-third of patients.[109]

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CHAPTER 22

Fetal and Neonatal Renal Function

Rakesh Rao and Akshaya J. Vachharajani

INTRODUCTION

The intrauterine function of transfer of solutes and removal of waste products is primarily carried out by the placenta. Although immature compared with the adult kidneys, fetal kidneys are uniquely adapted for their primary intrauterine function, i.e., to contribute to the amniotic fluid, and at the same time are capable of regulating fluid, solute, and water balance even at extremes of viable preterm gestation.

MORPHOLOGIC DEVELOPMENT

The excretory system's major role is allowing small molecules to form the blood to be excreted into urine and, at the same time, allowing reabsorption of water and electrolytes. Three evolutionary excretory systems can be identified (Figure 22.1):

1. *Pronephros*: One pair of kidneys consisting of a few primitive nephrons connected to the unbranched nephric duct, e.g., in invertebrates.
2. *Mesonephros*: Pair of kidneys that consist of a linear array of nephrons connected to the unbranched nephric duct, connected to the gonad in males, e.g., amphibians.
3. *Metanephros*: The nephrons are only indirectly connected to the nephric duct, as seen in higher mammals and humans.

In humans, the formation of the metanephric kidneys is preceded by the development and involution of the pronephros (day 22, eight- to nine-somite stage) and mesonephros in a temporal and anteroposterior sequence. All three originate from the intermediate mesoderm.

The pronephros contains rudimentary tubules opening into the pronephric duct that regress by the fifth week. The pronephric duct persists as a mesonephric duct (or Wolffian duct) and evolves into the ureteric bud (UB) (appears around the fourth to fifth week gestation) that is required for the formation of the metanephros. The mesonephros appears caudal to the pronephric tubules between the 3rd and 4th weeks and persists until about the 12th week of gestation. It is also the first definitive functioning kidney in humans characterized by the development of vascularized glomeruli-like structures connected to the proximal and distal tubules that drain into the mesonephric duct. The renal vasculature is primarily derived from the progenitor cells in the metanephric mesenchyme (MM).[1]

In males, the mesonephric duct gives rise to the vas deferens and epididymis, whereas they involute completely in females. The mesonephric ductules give rise to efferent ductules in males and can persist as epoöphoron and paroöphoron in females.

The metanephric kidney develops by reciprocal and sequential inductive interaction between the epithelial UB and the MM and reaches its final lumbar position by the eighth week of gestation.[2,3] The UB induces the formation of epithelial nephrons from the MM cells (mesenchyme-to-epithelial transformation [MET]), whereas the mesenchyme induces the UB to extend and branch (branching morphogenesis).[1,3,4] The UB draws the MM cranially to the final lumbar position of the kidneys by the eighth week of gestation.

Glial-derived neurotrophic factor (GDNF), a member of the transforming growth factor β (TGF-β) family, is the major growth factor secreted by the MM and acts via tyrosine kinase receptor *RET* (REarranged during Transfection proto-oncogene) and its coreceptor GFRα1; it is responsible for the proper positioning and branching of the UB. Mice lacking *Ret*, *Gdnf*, or *Gfrα1* develop renal hypoplasia or agenesis.[5–7] GDNF-RET signaling is positively regulated by several genes and factors, including *Hox11*, *Odd*, and *Pax2/8*. Transcription factors FOXC1 and FOXC2 secreted by the MM are important in regulating GDNF gradient. Sprouty 1 and Bmp4 also play important roles in UB branching. Other growth factors, including fibroblast growth factor (FGF), TGF-β, and Wnt family, are important in the MET process.[1,3,4,8]

The UB epithelium gives rise to the collecting system, including the collecting ducts, calyces, pelvis, ureter, and bladder trigone.[9] The MM differentiates into the glomeruli, proximal tubules, loop of Henle, distal tubular segments, and renal interstitium.[9] Two distinct processes occur concurrently resulting in the final renal architecture (architectonics and nephrogenesis) and are complete by 34–36 weeks of gestation. Renal growth beyond this period is a result of enlargement of the existing nephrons and the interstitial tissues. The renal vascular development parallels the patterns of growth of the UB and nephron formation and is completed by 15 weeks of gestation.

The renal architecture is predominantly determined by the branching pattern of the UB, which in turn determines the topographic distribution of the nephron. The UB first

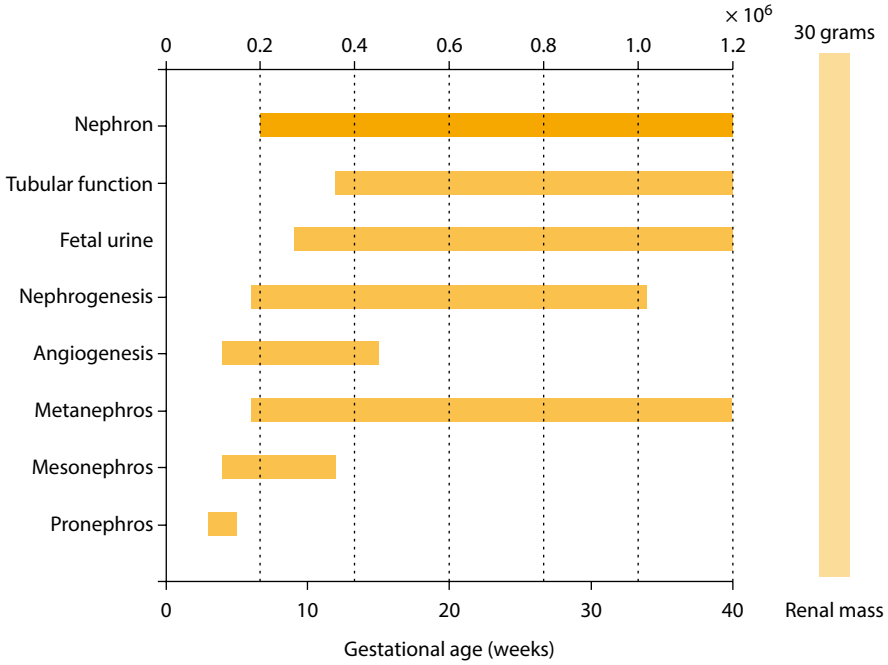

FIGURE 22.1 Schematic fetal renal development: The various aspects of renal development are shown. The UB appears around 5 weeks of age. By approximately 20 weeks of gestation, the fetal kidneys have 1/3 of the nephrons and 1/10 of the renal mass.

branches in a bifid manner, resulting in two daughter branches, although some lateral and trifid branching may occur until terminal bifid branching occurs. Each nephron connects to one ureteric tip, at which point branching ends. A small proportion of nephrons develop following a poorly understood late-phase branching.

Four distinct phases can be identified in the renal structural development based on the branching of the ampulla of the UB.

- *Period 1 (embryonic weeks 5–14)*: Ampullae actively divide and induce nephrons only when not carrying an attached nephron.
- *Period 2 (embryonic weeks 14–15 to 20–22)*: Ampullae rarely divide but induce nephrons when carrying an attached nephron—arcade formation.
- *Period 3 (embryonic weeks 20–22 to 32–36)*: Ampullae do not divide and induce nephrons only when not carrying an attached nephron.
- *Period 4 (embryonic weeks >36 to adulthood)*: Ampullae do not divide and do not induce nephron formation.

Similar to the formation of the renal architecture, nephron formation undergoes four distinct stages following the interactions between the UB and MM (Figure 22.2):

1. Condensation or aggregation: The MM cells aggregate around the UB tip (condensing mesenchyme).
2. Proliferation and development into renal vesicles.
3. Proliferation and development into comma- and S-shaped bodies.
4. Elongation and fusion with the duct.

The S-shaped body is a precursor to glomerulogenesis and tubulogenesis depending on the spatial segmentation of the S shape.[3,8] The proximal tubule and the loop of Henle arise from the lower and middle limbs, and the distal tubule from the upper limb of the S-shaped body, and fuse with the collecting duct. The first nephrons lie near the corticomedullary junction, and the last lie in the outer cortex.[1,3]

PHYSIOLOGIC ADAPTATION AT BIRTH

Body Composition

The predominant component of the human body is water, followed by solids (organs and tissues) and adipose tissue. Body water is distributed into several interconnected distinct compartments. Total body water (TBW) is the sum of all water present, both intracellular water (ICW) and extracellular water (ECW).[10–12] ECW consists of *plasma* (intravascular water), *interstitial fluid* (water surrounding the cells), and *transcellular water* (ECW enclosed by epithelial membrane, such as aqueous humor and cerebrospinal fluid, and water normally present in the respiratory, genitourinary, and gastrointestinal systems). Interstitial fluid volume is estimated as the difference between ECW and plasma (Interstitial fluid volume = ECW – plasma), and ICW as the difference between TBW and ECW (ICW = TBW – ECW).

In the fetus, TBW accounts for the majority of body weight. With advancing gestation, the fraction of TBW as a percentage of body weight of the fetus decreases as the amount of minerals and adipose tissue deposition increases (Figure 22.3). TBW accounts for almost 90% of body weight in the first trimester, ~86% at 24 weeks, 80% by 26 weeks of gestation, and approximately 75%–78% at term. This decrease in TBW is at the expense of a decrease in ECW and an increase in ICW. The decrease in ECW

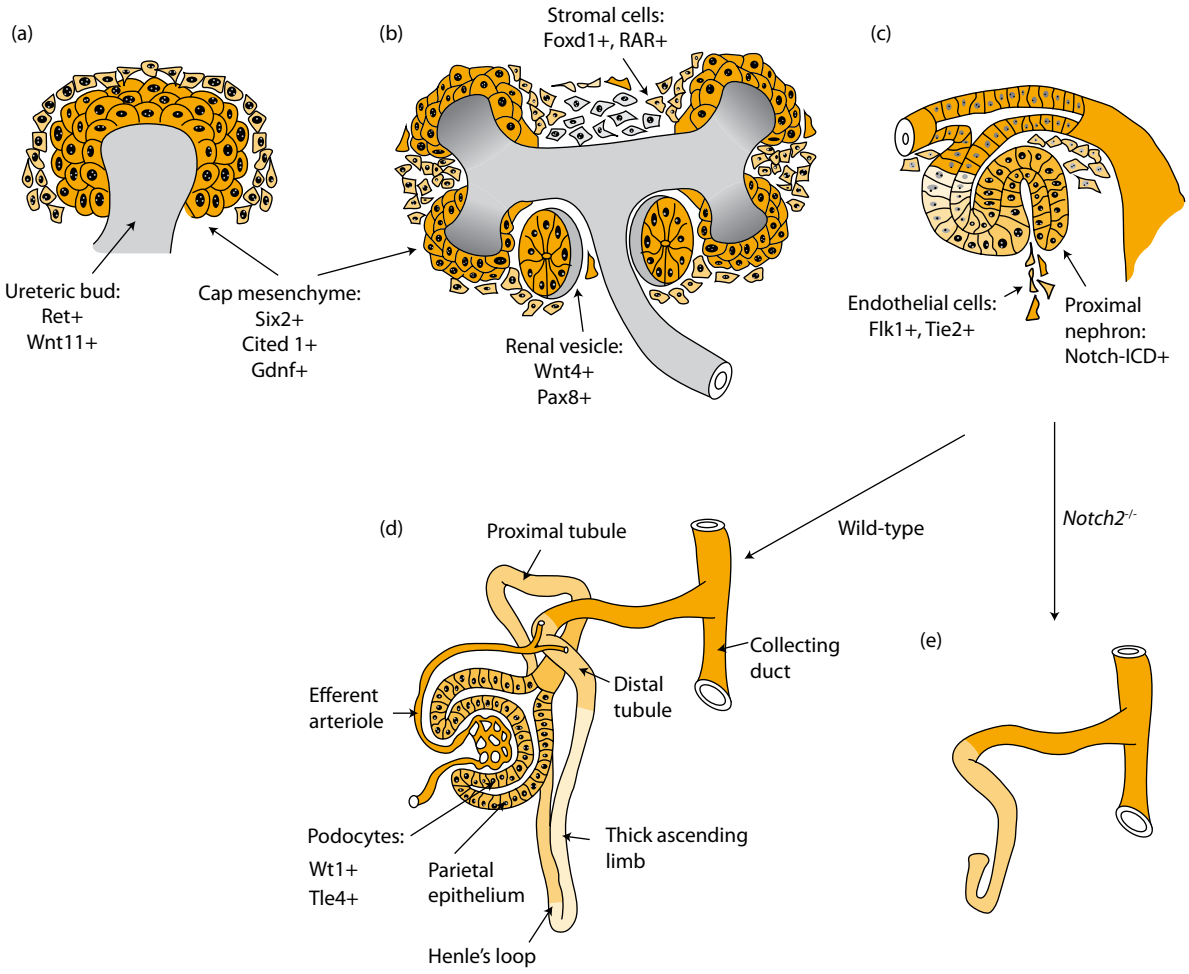

FIGURE 22.2 Nephron development and associated markers. (a) Invasion of UB (gray) and MM (orange). (b) Formation of renal vesicle from the cap mesenchyme. (c) Formation of ureteric stalk that forms the collecting duct and develops the S-shaped body with proximal and distal clefts. (d) Formation of nephron with glomerulus, elongation of proximal tubules, and loop of Henle. (e) Notch signaling determines the proximal-to-distal pattern of the nephron. (Adapted from Dressler GR. *Development* 2009;136(23):3863–74.)

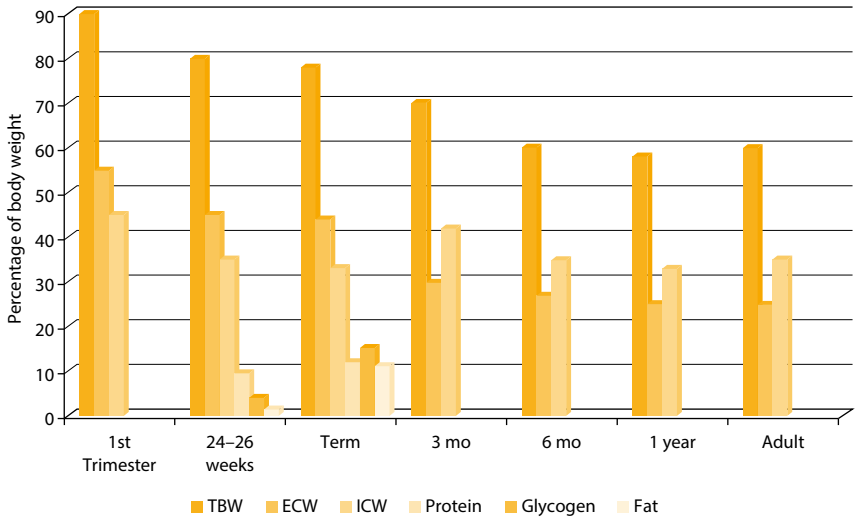

FIGURE 22.3 Contribution of body water compartments shown as a percentage of body weight. The TBW and ECW contributions to body weight decrease with advancing GA. Note the increase in glycogen, fats, and protein with GA.

is due to a decrease in interstitial fluid volume, as plasma volume (as percent of body weight) remains relatively constant across all ages. TBW accounts for 50%–70% of body weight in adults and varies inversely with body fat content. Obese people and women have a higher fat content, and therefore lower TBW.

TBW reaches adult values by 1 year of age (60% of body weight in males and 50% in females). There are similar changes in ECW distribution, with ECW accounting for 60% of TBW at 24 weeks and 44% by term.[13] Therefore, in a healthy term newborn TBW accounts for about 75%–78% of body weight, of which 44% is ECW, 34% is ICW, and 22% is solids. In adults, TBW is ~60% of body weight (ECW = ~33% of TBW) and ECW is ~20% of body weight.

After birth, there is a decrease in TBW that is disproportionately due to loss from the ECW compared with the ICW, particularly in the appropriately grown (appropriate for gestational age [AGA]) preterm infant. This loss from the ECW is due to loss of interstitial fluid without loss of plasma volume. The weight loss secondary to this postnatal diuresis is inversely related to the gestational age (GA) at birth; i.e., the lower the GA, the higher the weight loss. The exact reason for this diuresis remains debatable, but of importance in premature infants, the lack of adequate diuresis and weight loss is associated with worse morbidities, specifically that of bronchopulmonary dysplasia (BPD). In contrast to AGA preterm infants, small for gestational age (SGA) infants have less postnatal weight loss after birth, which has been ascribed to catabolism rather than shrinkage in the ECW compartment.[14] Delayed cord clamping that helps to increase total body iron stores in premature infants may result in an increase in plasma volume.

RENAL BLOOD FLOW AND GLOMERULAR FILTRATION RATE

Renal blood flow (RBF) and the glomerular filtration rate (GFR) in the fetus are low compared with those in adults and can be attributed to the smaller kidney size, decreased number of glomeruli, lower systemic pressure, and high renal vascular resistance. Effective renal blood flow (ERBF) measured using p-aminohippuric acid (PAH) may underestimate RBF as the renal extraction of PAH is decreased in the first 3 months of life (due to shunting of blood to the non-PAH-extracting tissues).

The fetal kidneys receive less than 5% of the fetal cardiac output, which increases to ~15% of the total cardiac output after birth and reaches 25% by adulthood. In utero, RBF (measured by color-pulsed Doppler flow) increases exponentially between 20 and 40 weeks of gestation by nearly 10-fold in conjunction with nephrogenesis. RBF increases with GA and is higher in adults than in newborn infants. Interestingly, the increase in RBF after birth correlates with postconceptional age rather than postnatal age.[15] ERBF increases from 20 mL/min/1.73 m^2 at 30 weeks of gestation to 45 mL/min/1.73 m^2 by 35 weeks of gestation, and to 83 mL/min/1.73 m^2 at term. By 3 months of age, ERBF increases to 300 mL/min/1.73 m^2, and to 650 mL/min/1.73 m^2 by 12–24 months of age.[16,17]

The glomerular arterioles are the primary site of renal vascular resistance that determine the renal as well as the intrarenal distribution of blood flow. Blood flows into the glomerulus via the afferent arteriole that arises from the interlobular artery and exits via the efferent arteriole. With advancing GA, renal blood increases to all areas of the kidney: the cortex (containing the glomeruli), medulla (tubules and the vasa recta), and papillary area. The neonatal kidney, compared with the adult kidney, receives more blood in the inner cortical and the medullary area than the outer cortical layer. RBF is also dependent on arterial blood pressure and the blood volume.

After birth, renal vascular resistance decreases and RBF increases. The increase in RBF is dependent on changes in cardiac output, perfusion pressure, and renal vascular resistance, as well as the presence of vasoactive substances, rather than on anatomic factors alone, as nephrogenesis is complete before term birth in humans (but continues in dogs and rodents). Vasoactive substances act by altering the participation of the vascular beds (interlobular, afferent, and efferent arterioles) and affecting the intrinsic myogenic responses of the resistance vessels that are unique to the immature kidney.[17] Several vasoconstrictive substances (endothelins, renin angiotensin system, and arginine vasopressin) and vasodilators (adenosine, nitric oxide [NO], bradykinin, and natriuretic peptides) act together to modulate RBF, as discussed further briefly below (Table 22.1).

Angiotensin II is one of the most potent vasoconstrictors in the immature kidney. Circulating levels of renin and angiotensin II are higher in the more immature kidney and decrease after birth. Angiotensin II acts via the angiotensin receptors AT 1–4, of which AT-1 and AT-2 may also be involved in renal angiogenesis and nephrogenesis. AT-1 receptors cause vasoconstriction and are expressed in the kidney on the glomerulus, arterioles, and medulla, and its gene expression increases after birth; the expression of AT-2 is seen earlier in gestation, and its expression decreases after birth.[19,20] AT-1 receptor antagonists produce renal defects similar to those seen with intrauterine exposure to angiotensinogen-converting enzyme inhibitors, and disruption of AT-1 and AT-2 receptors leads to malformations of the kidney and urinary track. In lambs, inhibition of AT-1 receptor, but not AT-2 receptor, causes a decrease in renal vascular resistance and an increase in RBF.[17]

NO, produced by the vascular endothelium, is a potent vasodilator. Nitric oxide synthase (NOS) is present as distinct isoforms: in the endothelium (eNOS) and as inducible (iNOS) and neuronal (nNOS) nitric oxide. NO production is most abundant in the immature kidneys compared with adults, with nNOS being expressed abundantly in the cortex and the medulla. Blockage of NO production causes renal vasoconstriction that is mediated via angiotensin II.[21,22]

RBF remains constant despite alterations in renal perfusion pressure (autoregulation), although over narrower ranges with decreasing gestation. With increasing maturity, autoregulation of the RBF is also determined by the relationship between the GFR and tubular flow (tubuloglomerular feedback). As the GFR increases, the tubular flow and responses also increase, so that the relative sensitivity of the feedback mechanisms remains relatively unchanged.[17]

TABLE 22.1 Vasoactive substances in the kidney

	Action	Site	Effects
Adenosine Regulates intrarenal blood flow	Vasodilator A1 receptor: Inhibits renin release and afferent vasoconstriction A2: Stimulates renin release and afferent/efferent dilation	Increases medullary against cortical blood flow via the A2 receptor Increases RBF and decreases efferent vascular resistance	Tubuloglomerular feedback Protect medulla from hypoxic injury
Bradykinin Intrarenal vasodilator	Opposes action of angiotensin II in the immature kidney?		Role in maturational increase in RBF?
Endothelins 3 peptides, ET 1–3	ET-1: Afferent and efferent arteriolar constriction via ETA receptors ET-2 ET-3	ETA receptor in tunica intima: Vasodilation ETB receptor in tunica media: Vasoconstriction	ETB1 receptor: Vasodilator ETB2 receptor: Vasoconstrictor
Arginine vasopressin	V1a receptor: Arteriolar vasoconstriction	Glomerular and arteriolar	
Atrial natriuretic peptide	Atria and ventricles: Respond to volume	Proximal and distal tubules	Renal vasodilation, decrease blood pressure Increase RBF and GFR Inhibit Na and water reabsorption and urine concentration
Angiotensin (1–7)[19]	Site specific	Proximal tubules, renal vascular cells, and glomerular epithelium	Vasodilation of preconstricted afferent arterioles (via NO) Blocks transcellular sodium transport Counteracts angiotensin II–mediated hypertrophic effects

Fetal GFR increases in parallel to the increase in RBF, from <1 mL/min at 20 weeks' gestation to 5 mL/min at term.[15] This increase is attributable to the increase in surface area of the glomerular basement membrane determined by the number and degree of maturation of glomeruli as they limit the amount of fluid that can be filtered.[23] Further, GFR is also dependent on the RBF, blood volume, arterial blood pressure, and glomerular permeability. GFR at birth is proportional to the GA (Figure 22.4); however, regardless of GA, the GFR doubles within 2 weeks of birth, attributable mostly to the increase in the net filtration pressure and ultrafiltration coefficient.[24] In very low-birth-weight infants, catch-up in GFR may take several months.[15] Genetic and environmental factors can affect fetal GFR; for example, antenatal exposure to angiotensinogen inhibitors (captopril and enalapril) and prostaglandin (PGE) inhibitors (indomethacin) reduces GFR.[25]

Tubular Handling of Sodium and Potassium

Sodium and potassium accretion are important for fetal and neonatal growth. However, the regulation of sodium and potassium and their transport vary.

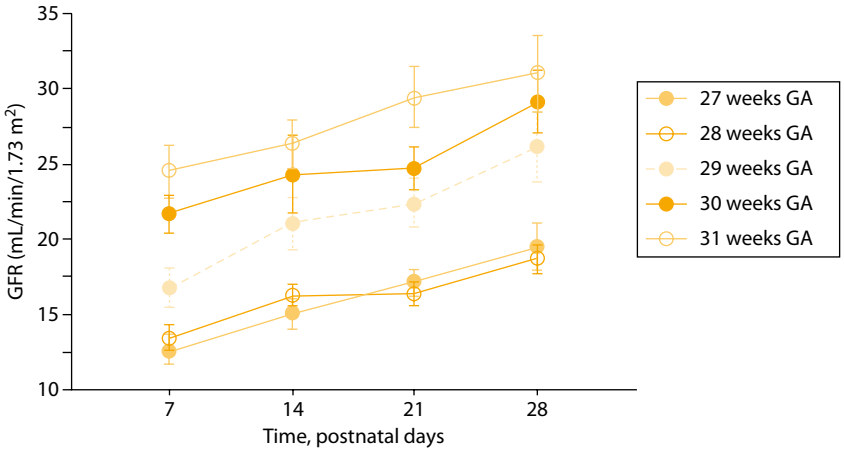

FIGURE 22.4 GFR in preterm infants is inversely proportional to the GA. (From Vieux R et al. *Pediatrics* 2010;12(5):e1186–92. With permission.)

Sodium handling by the kidney depends on the stage of fetal and neonatal maturity. The fractional excretion of sodium (FE_{NA}) measures the tubular sodium transport that is "normalized" for the GFR. FE_{NA} is calculated by

$$\frac{\left(\begin{array}{l}\text{Urinary concentration of sodium } (U_{NA}, \text{mEq/L}) \\ \quad \times \text{Urine volume/unit time}\end{array}\right)}{\left(\begin{array}{l}\text{Creatinine clearance} \\ \quad \times \text{Plasma sodium concentration } (P_{NA}, \text{mEq/L})\end{array}\right)}$$

or

$$FE_{NA} = (U_{NA} \times P_{cr}) / (U_{cr} \times P_{NA}) \times 100\%$$

FE_{NA} varies inversely with GA and with postconceptional age. Fetal FE_{NA} is very high, with an average of 12.8%. However, before 30 weeks' gestation, FE_{NA} is 5%, but it approaches 1% by term gestation, signifying improving renal maturity for sodium conservation. In fact, this high FE_{NA} puts the fetus of <30 weeks' gestation in a state of negative sodium balance, and it only approaches a positive balance by 36 weeks' GA. When infants are born preterm, the sodium balance is dependent on the severity of prematurity and the degree of sickness. For example, Vanpee et al. noted that the FE_{NA} declined rapidly after birth for infants born at 25–30 weeks' GA and 31–34 weeks' GA and approached term newborn levels by 4–6 weeks after birth.[26] In healthy preterm infants of >33 weeks' gestation, a positive sodium balance is seen by days 2–4 of age, in contrast to sick preterm infants, where higher FE_{NA} and negative sodium balance can persist beyond a week of age.[27] The FE_{NA} in healthy term newborn infants is <1% by 24–48 hours of age.

A negative sodium balance impacts *postnatal* growth, particularly in very low-birth-weight infants. However, while supplementation can prevent late hyponatremia, excessive sodium administration can result in water retention and an increase in ECW. As mentioned previously, lack of adequate diuresis in this population has been associated with an increased risk of BPD.[28]

In preterm infants, both proximal and distal tubular reabsorption of sodium is inversely related to GA. Both in preterm and term infants, the ability to achieve diuresis in response to a renal sodium load is limited compared with in older children due to the functional immaturity of the distal tubule, the site that is primarily responsible for the developmental and postnatal maturation for renal conservation of sodium.[29] In preterm infants of <34 weeks' GA, distal sodium reabsorption is higher, but the fractional distal sodium reabsorption is decreased compared with in term infants during maximal water diuresis.[30]

Since sodium is freely filtered at the glomerulus, several mechanisms at various parts of the nephron act to conserve sodium. In the proximal convoluted tubule (PCT), the fractional reabsorption of sodium remains relatively constant at ~60% by both active and passive mechanisms. The latter is due to the presence of a relatively permeable tubular epithelium and lower tubular hydrostatic and oncotic pressures that allow for passive reabsorption of sodium and other solutes.

Several transport proteins are responsible for the active transport of sodium.[31–33] In the PCT, the expression of the basolateral Na^+ K^+ ATPase pump produces the electrochemical gradient for Na^+ reabsorption. The activity of the Na^+ K^+ ATPase pump and the capacity for active transport increase nearly threefold with advancing gestation and are positively upregulated by aldosterone and glucocorticoid exposure. Further, the distribution of the Na^+ K^+ ATPase pump is also developmentally regulated with differential expression of the β_1 (basolateral, upregulated) and β_2 (apical, downregulated) subunits.

Symporters (family of proteins that transfer solutes from the lumen to the tubular cells) also play an important role in the reabsorption of solutes, such as bicarbonate and phosphate coupled with sodium reabsorption. The sodium hydrogen exchangers (NHEs), a family of membrane proteins (NHE 1–4), are the major transporters of Na^+ in the PCT. They are expressed in the kidneys and gastrointestinal tract, including the stomach, and regulate intracellular pH (NHE-1), sodium (NHE-2 and NHE-3), and bicarbonate (NHE-3) reabsorption. NHE 1, 2, and 4 are amiloride sensitive, whereas NHE-3 is not. Homozygous mutant NHE-3 knockout mice have diarrhea and mild acidosis but are not significantly hyponatremic due to upregulation of aldosterone and colonic epithelial Na^+ and H^+ K^+ ATPase.[34]

Other transporter proteins that contribute to the reabsorption of Na^+ in the PCT include the sodium bicarbonate transporter (NBC) family of proteins (NBC 1–3), which transport Na^+ and HCO_3^- bicarbonate, and the sodium-phosphate Type IIa (Na-P_i) cotransporter, which is rate limiting for cotransport of Na^+ and phosphate. The Na-P_i cotransporter is expressed more robustly in newborn than mature animals and is upregulated in NHE-3 knockout mice.

The thick ascending loop of Henle (TALH) only has 20% absorptive capacity for Na^+ compared with adults due to the lower Na^+ K^+ ATPase activity; thus, more isotonic fluid is delivered to the distal tubule, and with limited absorptive capacity, the urinary concentrating ability in the premature infant is limited.

The epithelial sodium channel (EnaC) expressed on 70% of the distal convoluted tubules and the cortical collecting duct are the principal sites for electrogenic Na^+ transport in the distal nephron. Four functional subunits of EnaC channels (α, β, γ, and δ subunits) have been identified that are present in the lungs and kidneys. The EnaC channels are the ratet-limiting step for Na^+ reabsorption and primarily mediated via aldosterone by binding to its (mineralocorticoid) receptor.[35–37] In experimental aldosterone-sensitive cell lines (A6), aldosterone regulates sodium reabsorption via activation of EnaC through the expression of the small G-protein K-Ras2A in the short term and by regulating the trafficking and degradation of EnaC in the long term. EnaC knockout model mice develop salt wasting and metabolic acidosis and have difficulty clearing lung fluid.[32]

Other cation-Cl^- cotransporters (CCCs) include the chloride-coupled transporters that cotransport Cl^- with Na^+ or K^+, such as the furosemide-sensitive Na-K-Cl cotransporters (NKCC 1 and 2), Na^+-Cl^- cotransporter (NCC), and K^+-Cl^- (KCC) cotransporters and the CCC

interacting protein (CIP).[32] The Na-K-Cl cotransporter expressed in the TALH is responsible for Na^+ and Cl^- transport, and the KCC are inhibited by loop diuretics (see the "Potassium" section below). Lastly, the thiazide-sensitive NCC is the primary determinant of sodium and chloride reabsorption in the distal nephron.

The expression and distribution of renin in the kidneys are spatially and temporally regulated in relation to vasculogenesis. Renin-expressing cells are initially present all along the interlobar and arcuate arteries in the fetus but are limited to the juxtaglomerular portion of the afferent arteriole in adults.[38] Angiotensin-converting enzyme (ACE) inhibitors or angiotensin II antagonist exposure in utero causes a decline in the fetal GFR (reversed by angiotensin II) with an increase in RBF; the fractional reabsorption of Na^+ in the proximal tubule is, however, not affected.[39] Interestingly, the activity of angiotensin II appears to be independent of aldosterone secretion.

Plasma renin activity (PRA) and plasma aldosterone (PA) concentrations are highest in the newborn period. In preterm infants, the lack of exogenous sodium supplementation results in a rapid rise in PRA and PA activity, followed by a more gradual decline. PRA is also inversely correlated with urinary sodium excretion in term infants.[40] Urinary aldosterone excretion (UAE) is similar in preterm and term infants and is higher than in adults.[41] In term but not preterm infants, the urinary Na/K ratio can be used to assess the effect of aldosterone on tubular function, and it has a linear relationship with UAE. The high UAE also corresponds to the period of hyponatremia seen in the preterm infants in the first 2 weeks of life. Further, the renal response to aldosterone is blunted in preterm infants compared with term infants at the postreceptor level.

PGE is a regional vasodilator and counteracts the vasoconstrictive effects of the renin–angiotensin system; use of PGE antagonists like indomethacin can result in decreased renal and glomerular blood flow and GFR. Sodium supplementation decreases PGE activity.

Lastly, sodium and water reabsorption are also mediated via catecholamines, atrial natriuretic peptide, and digoxin-like substances.[32]

Potassium

Potassium is the most abundant intracellular cation, with an intracellular concentration of 100–140 mEq/L maintained by the Na^+ K^+ ATPase pump. The Na^+ K^+ ATPase pump by active cytosolic hydrolysis of ATP extrudes three molecules of Na^+ for the uptake of every two molecules of K^+. Muscles are the primary intracellular reservoir, with 98% of total body potassium; the remaining 2% is distributed in the extracellular fluid.

Potassium is conserved by the fetus for growth, particularly after 30 weeks' gestation. Postnatal growth is associated with an increase in total body potassium from 8 to 14 mEq/cm body height from birth to adulthood, respectively. Fetal potassium concentrations are maintained above 5 mEq/L; newborn infants therefore have higher plasma potassium concentrations at birth, with higher levels in the more immature (up to 6.5 mEq/L). The urinary Na/K ratio in the newborn may exceed 1 (normal 0.5–0.6) up to 4 months of age in term infants and may be >2 in infants of <34 weeks' gestation due to relative nonresponse to mineralocorticoids in preterm infants.[42]

Extremely preterm infants, <28 weeks, develop nonoliguric hyperkalemia (>6.5 mEq/L) within 48 hours of birth, even without any potassium intake. Low Na^+ K^+ ATPase pump activity, limited renal potassium secretory capacity, and developmental expression of potassium transporters may all play a role.[42] The nonoliguric hyperkalemia is, however, not seen in the more mature or term infants. Antenatal steroids for fetal lung maturation also cause maturation of the Na^+ K^+ ATPase pump and may prevent this phenomenon.

Adults excrete 90%–95% of daily potassium intake via urine (90%) and stool (5%–10%), with nearly 50% of an oral load excreted within 4–6 hours of ingestion. Renal secretion, rather than reabsorption, is the dominant mechanism of potassium homeostasis in a fully mature kidney.

In contrast, renal potassium clearance and excretion per unit body weight or kidney weight is lower in newborn infants even when corrected for the lower GFR. However, in response to potassium challenge, newborn infants are capable of secreting potassium, albeit at lower rates than adults. The fractional excretion of potassium is reduced by 50% between 26 and 30 weeks' GA despite a near threefold increase in the filtered load of potassium during this period, suggesting that the immature kidneys are also capable of reabsorbing potassium.[44]

Potassium is freely filtered into the glomerulus, and nearly 65% is passively reabsorbed, along with sodium and water in the PCT. The TALH, which absorbs potassium in adults, is not fully mature in newborn infants. The cortical collecting ducts are the final site of K^+ excretion but are limited in their capacity to excrete K^+ in newborn infants compared with adults.[45–47] Data from rodent experiments suggest that nearly 35% of the filtered potassium load reaches the distal tubule in 2-week-old rats, compared with 10% in human adults. The absorption of potassium in the TALH is regulated by the Na^+, K^+, and $2Cl^-$ cotransporter (blocked by loop diuretics, such as furosemide and bumetanide) along an electrochemical gradient created by the basolateral Na^+ K^+ ATPase. The activity of the Na^+ K^+ $2Cl^-$ transporter also requires the presence of a luminal secretory potassium channel encoded by the rat outer medullary K^+ channel (*ROMK*) gene. Loss-of-function mutation of the ROMK gene is associated with neonatal Bartter's syndrome (polyhydroamnios, salt wasting and dehydration, hypercalciuria, hyperreninism, hyperaldosteronism, and normal blood pressure presenting in the first week of life).

Potassium secretion in the collecting duct and the distal tubule contributes to the urinary potassium excretion and can approach 20% of the filtered load in adults. The *principal cells* are primarily responsible for the absorption of Na^+ and K^+, while the *intercalated cells* absorb K^+ in response to potassium restriction or acidosis.[45] In the principal cells, Na^+ K^+ ATPase transports K into the cell at the expense of Na^+ to build a concentration gradient, thus allowing K^+ to passively diffuse out into the lumen via two secretory channels: (1) the small-conductance (SK) channel encoded by the *ROMK* gene that mediates baseline potassium secretion, and (2) the high-conductance calcium- and stretch-activated maxi-K channel that regulates

flow-stimulated potassium secretion.[45] Potassium reabsorption in the distal kidney is regulated by the H^+ K^+ ATPase localized in the intercalated cells.

The postnatal increase in potassium secretory capacity is due to developmental increase in the expression of both the SK and maxi-K channels.[47,48] In newborns, potassium secretion in the distal cortical collecting duct cannot be stimulated by increasing the urinary flow rate. Thus, volume expansion or increases in tubular flow rate by diuretics do not increase K^+ secretion in the immature kidney.[45]

Calcium and Phosphorous

In addition to regulating Na^+ and K^+, the kidney also plays an important role in regulating calcium and phosphorous homeostasis.

Ca^{++} is the most abundant mineral in the human body, accounting for almost 2% of total body weight. Calcium deposition within the bones accounts for 98% of total body calcium and is predominantly deposited in the third trimester of pregnancy, along with phosphorous. The kidneys regulate Ca^{++} absorption and excretion in parallel with Na^+ under various conditions, such as acidosis or alkalosis, diuretics use, and alterations in volume status. Less than 2% of the filtered calcium is excreted in the urine, with the majority absorbed by passive transport via the intercellular spaces in the PCT (70%) and the TALH (20%) by voltage-driven paracellular flux; the remaining is reabsorbed by active transcellular transport in the distal convoluted and connecting tubules (10%–15%).[49] The latter is the primary regulator of body Ca^{++} balance and is independent of Na^+ balance.

Active transcellular Ca^{++} transport is a complex multistep process requiring entry via the apical epithelial calcium channels, cytosolic buffering by calcium binding proteins (calbindin-D_{28K}), facilitated diffusion to the basolateral side, and finally, extrusion into the vascular interstitium by sodium calcium exchanger (NCX1) and plasma membrane calcium adenosine triphosphatase (PMCA1b).[49] The first step is the rate-limiting factor regulating calcium reabsorption in the distal tubules.

The epithelial Ca^{++} channel (TRPV5), a member of the transient receptor potential (TRP) channel proteins, is a highly Ca^{++}-selective channel responsible for Ca^{++} influx in epithelial cells and expressed on the apical membrane in the distal convoluted tubule (DCT) and connecting tubule. TRPV5 is responsible for active reabsorption of Ca^{++}. TRPV5 is ubiquitously expressed in the kidneys, intestine, pancreas, brain, prostrate, and testes, and homozygous knockout mice exhibit hypercalciuria, intestinal hyperabsorption of Ca^{++}, and reduced bone thickness. The expression of the TRPV5 gene in turn is regulated by vitamin D3, parathyroid hormone (PTH), and the antiaging hormone Klotho.[50] The calcium-sensing receptor (CaSR), originally described in the parathyroid gland and also expressed in the kidneys, is the major receptor through which extracellular effects of Ca^{++} are mediated. In the developing human kidney, CaSR is expressed on the TALH and distal tubules and inhibits the paracellular absorption of calcium in the TALH.[51]

Phosphorous is present mostly in the bones (80%), two-thirds of which is present as organic phosphorous (esters and phospholipids) and one-third as inorganic phosphate (in plasma bound to calcium, magnesium, or protein). Plasma concentrations of phosphate are highest in neonates compared with children and adults. The nonprotein-bound fraction of phosphate (~90%) is freely filtered across the glomerulus, and 75%–85% of the filtered phosphate load is reabsorbed in the PCT. The remaining is excreted as titrable acid in urine. A small fraction is reabsorbed in the distal collecting or connecting tubule in adults.

The tubular reabsorption of phosphate is a saturable process and is dependent on the GFR. However, despite the low GFR in newborn infants, phosphate reabsorption is increased and urinary excretion limited in periods of growth in the preterm infants despite high plasma phosphate levels. Phosphate reabsorption is also higher in the deeper juxtamedullary nephrons than in the more superficial nephrons, and likely contributes to the higher phosphate reabsorption in utero. In states of phosphate conservation, reabsorption of phosphate also occurs in the DCT, the proximal straight tubule (pars recta), and the collecting tubule, but not in the loop of Henle, due to low permeability. As mentioned previously, phosphate transport is coupled with sodium via the Na^+-dependent Pi family of cotransporters (Na-Pi Types I–III). Of these, the Na-Pi Type II family (IIa, IIb, and IIc) is most involved in regulating Na^+ and phosphorous transport, particularly the Type IIa isoform expressed in the proximal tubule.[52,53] The increase in tubular reabsorption of phosphorous may be directly related to the increase in the expression of this isoform with increasing maturation. Several other factors, including thyroid, parathyroid, and growth hormones; dietary phosphate intake; and phophatonins (autocrine–paracrine factors that affect tubular phosphate uptake), such as FGF23, also influence renal phosphate regulation.

Although transfer across the placenta is the major source of protein deposition in the fetus, the kidneys also play an important role in regulating amino acid and organic acid homeostasis. The PCT is the primary site for reabsorption of amino acids following glomerular filtration. With the exception of taurine and glycine, nearly 80% of the filtered amino acids are reabsorbed by active processes across the tubular luminal brush border with little passive diffusion.[54,55] Following intracellular active transport across the apical membrane with Na^+- or H^+-coupled symporters (the Na^+ neutral amino acid transporter B^0 AT-1 transports 80% of free plasma neutral amino acids), amino acids mostly passively efflux across the basolateral membrane. The basolateral Na^+ K^+ ATPase pump actively pumps Na^+ out of the tubular cells into the intercellular space, creating a concentration gradient at the brush border for Na^+ to enter the cell from the tubular lumen and cotransporting amino acids with it. Since most amino acids are transferred by non–amino acid–specific group cotransporters, disease states such as cystinuria result in additional loss of arginine, ornithine, and lysine. Preterm infants are often noted to have *developmental aminoaciduria*, with failure to reabsorb amino acids in the PCT likely from differential maturation of the brush border transporters that allow for amino acids and Na^+ influx and mechanisms that allow for amino acid efflux from the cell into the perivascular blood vessels.[56] Several groups of

amino acid transporters have been identified at the brush border, of which the Na^+- and Cl^--dependent transporters (GAT family) are the most important. Others include the cationic amino acid transporters (CAT family), glutamate transporters, and cationic neutral amino acid transporters (rBAT family). Immaturity of the brush border absorptive mechanisms may result in amino acid deficiency, such as taurine, which becomes conditionally essential in preterm infants.

Organic acids, such as hippuric acid, uric acid, and antibiotics (coupled with organic acid transporters), are actively secreted by the PCT. Several organic acid–specific (OAT), urate-specific (URAT), and organic cation–specific (OCT) transporters allow for active transport of organic acids against a concentration gradient.[57–59] An increase in RBF and GFR, in addition to the increase in the expression of these transporters, results in an increase in tubular transport capacity and an increase in urine organic acid excretion with advancing GA. Elimination of organic drugs by renal tubular secretion, such as penicillin, is therefore maturation dependent.

URINE CONCENTRATION AND DILUTION

Although the fetal kidneys are capable of concentrating and diluting urine, albeit not similar to adults, the primary purpose of fetal urine production is to provide adequate amniotic fluid volume: the excretory functions are carried out by the placenta. Fetal urine is hypotonic compared with fetal plasma. After birth, the kidneys conserve water and excrete a solute load under healthy and diseased states.

Anatomical, functional, and developmental differences contribute to the limited fetal and neonatal renal function. Shorter loops of Henle, limited salt reabsorption in the ascending loop of Henle, greater medullary RBF per nephron compared with the cortex despite a higher cortical-to-medullary blood flow, and limited fetal response to antidiuretic hormone (ADH) (discussed below) are some of the factors that limit the efficacy of the medullary osmotic gradient necessary to concentrate urine fully in the fetus and neonates compared with an adult. Detailed reviews of the mechanisms of urine concentration and dilution are available[60,61] and discussed briefly below.

The movement of water from the tubular lumen and along the interstitial gradient depends on ADH and the tubular vasculature. The development and maintenance of the interstitial osmotic concentration gradient is determined by urea. Vasopressin increases urea permeability in the terminal inner medullary collecting ducts by increasing expression of the urea transporters (UT-A1 and UT-A3).[61] Fluid absorption in the PCT is isotonic; concentration occurs primarily in the loop of Henle and the collecting tubules. In the latter, water is absorbed along an osmolar gradient under the influence of ADH and by active NaCl absorption in the thick TALH.

The TALH in the outer medulla is capable of absorbing NaCl in the relative absence of water, resulting in the dilution of the tubular fluid; TALH is also impermeable to water, thereby allowing the urine to be more dilute and more isotonic as it enters the distal convoluted and collecting tubules. Vasopressin stimulates NaCl reabsorption by the medullary TALH, while it induces water reabsorption from the outer medullary collecting ducts. These actions result in an osmotic gradient and reabsorption of water from the collecting tubules in the outer medulla.

Fetal ADH, expressed by 12 weeks' gestation, is an important regulator of fetal urine production, as the placenta is impermeable to maternal ADH. The urinary concentration increases with advancing gestation due to an increase in reabsorption of free water (under the influence of ADH) relative to the solute (urea). Although the fetal collecting duct expresses ADH receptors, fetal cAMP production in response to ADH is lower than that in adults due to the lower sensitivity to ADH or to a decreased number of ADH receptors. More recently, elevated phosphodiesterase levels have been suggested as the reason for the blunted response to ADH.[23] With advancing gestation, fetal ADH concentrations respond to fetal blood volume, hypoxia, and both osmotic and nonosmotic factors. ADH causes transplacental water retention by inhibiting flow from the fetus to the mother, and regulates fetal blood pressure by redistribution of blood flow to the brain, heart, and umbilical–placental circulations under conditions of fetal stress. Preterm infants with a larger extracellular free water content and relative hyponatremia have a blunted response to ADH in the first few weeks after birth.

Aquaporins (AQPs) (seven have been described in the kidneys so far)—transmembrane proteins expressed in the kidneys and other tissues—regulate water transport.[62] Their expression in the kidneys is developmentally regulated, and they have specific cellular localization. They may or may not be under hormonal control.

AQP-1 expressed in the proximal tubules in the S1, S2, and S3 segments is a major transmembrane pathway that imparts high osmotic water permeability but is not under hormonal control (i.e., ADH). Mice deficient in AQP-1 are polyuric and cannot tolerate water deprivation. AQP-1 expression is decreased at birth compared with in adults. In contrast, AQP-2, expressed on the principal cells in the outer and inner medullary collecting ducts by 20 weeks' gestation, is regulated by ADH, mediates short-term responses to ADH, and plays a role in long-term adaptation to stimuli. For example, AQP-2 downregulation is seen with prolonged lithium use, ureteric obstruction, and chronic hypokalemia and hypercalcemia. In preterm infants, postnatal diuresis is associated with increased AQP-2 excretion in the urine.[63,64] The increasing fetal sensitivity to ADH with advancing GA is due to increased expression of AQP-2. AQP-3 is also present on the principal cells in the collecting ducts and is the major site for osmotically driven water movement. Prolonged water deprivation results in upregulation of AQP-3 expression. AQP-6 is expressed in intracellular vesicles in the intercalated cells of the collecting duct, and AQP-11 is expressed in the endoplasmic reticulum in the proximal tubules. Knockout mice deficient in AQP-11 develop polycystic kidney disease.[62]

The renal medulla is the primary site for urine concentration and dilution. The concentration of urine requires two distinct steps: extraction of water via the water channels (AQPs) and solute (chloride or urea) movement from the ascending loop of Henle (via chloride channels) to the

medullary interstitium to provide a concentration gradient. The countercurrent multiplier system (and the vasa rectae) allows the medullary interstitium to be progressively hypertonic at the same time, allowing osmotic equilibration between the medullary collecting duct fluid and the medullary interstitium. The thin ascending limb of the nephron is permeable to Cl^- and expresses the chloride channel ClC-K1, which allows efflux of NaCl and concurrent water into the interstitium, thus increasing the osmolality of the collecting duct fluid. The absence of this channel results in diabetes insipidus in rats.[65] The expression of the ClC-K1 channel is developmentally regulated and increases with gestation; maturation of this channel allows the establishment and maintenance of the medullary interstitial gradient.

Urea, the final metabolite of protein breakdown, accounts for nearly 50% of the solute load in a maximally concentrated urine. Neonates have lower urea content in the urine (likely from increased utilization for growth) than adults, although the nonurea solute contents are similar. However, when given a protein load, newborn infants can increase their maximal urine osmolality independent of fluid intake or urine output.

Although vasopressin levels are elevated at birth in both preterm and term infants, developmental differences (see above) in ADH concentrations and responses can explain some of the limited concentration capacity of the newborn kidney. In addition, AQPs, PGEs, and an intact renin–angiotensinogen axis play important roles in urine concentration.

Multiple factors in the newborn period contribute to the relative inability of newborn infants to concentrate urine; both preterm and term infants are able to concentrate urine more than 600 mOsm/kg soon after birth.[66,67] Term infants reach adult levels by 2 years of age.[23] The renal concentration capacity for urine is directly dependent on the length of the loops of Henle as they descend into the medulla. In rabbits, a postnatal increase in the length of the loops of Henle results in more than doubling of the urine concentrating capacity by 3 weeks of age. Newborn infants have a shorter length of the loops of Henle and relatively short papillae that increase with maturation. The shorter loops of the superficial nephrons (that mature last) allow accumulation of urea in the inner medulla. With increasing maturation, their elongation into the deeper cortical and outer medullary portion, accompanied by the vascular bundles, correlates directly with an increase in concentration ability. In addition, the renal inner medullary tubular organization is also different in neonates and adults. The thin descending loop of Henle is less permeable to water but capable of actively absorbing Cl^- (the ClC-K1 and Na^+-K^+-Cl2 channels) without water in newborns, thus allowing for excretion of more dilute urine. The inner medullary duct is also incapable of recycling urea, as the urea transporters (UT-A1) are lower in the neonatal period. In addition to these anatomic and morphologic differences, the RBF is preferentially distributed to the renal medulla and the glomerular blood flow is greater in the deeper than the superficial nephrons. In contrast, in adults, 90% of the RBF is through the cortex, 10% is through the outer medulla, and only 1%–2% reaches the inner medulla and papillae: this allows adult kidneys to maintain osmotic gradient secondary to the countercurrent system.

In the fetus and newborn, urine is hypotonic compared with the serum. By term, the fetal urine output is almost 5 mL/kg/h. The diluting capacity of the immature kidneys is similar to those of adults, and both can excrete 10%–15% of a filtered load, but this is limited by the lower GFR in newborn infants, which limits the amount of water that can be excreted. The ability to excrete a water load is clearly seen by the fact that infants after a week of age are capable of producing urine with a specific gravity of 1.002 when the GFR increases. Even in preterm infants, urine flow rates increase rapidly after birth to more than half the adult levels (12–14 mL/min/1.73 m^2) and urine osmolality reaches adult levels (50 mOsm/kg).

Thus, while the fetal renal capacity to concentrate urine increases with gestation due to an increase in concentrations and tissue response to ADH, an increase in water reabsorption capacity in the collecting tubules occurs as a result of increasing AQP-2 expression. The decreased concentration capacity is also limited by the inability of the fetus to generate and maintain a hypertonic medulla and an adequate osmotic gradient. Fetal kidneys respond to hypervolemia, hypoxia, and asphyxia by alterations in concentrations of ADH that under adverse conditions limit transfer of water across the placenta, maintaining adequate blood volume and blood pressure.

Postnatal

In healthy newborn infants, the renal concentration capacity increases exponentially after birth and reaches adult levels by 2 years of age. The maximal urine concentration in term newborns increases from approximately 515 mOsm/kg in the first week of life to 800–900 mOsm/kg by 1 month and to more than 1100 mOsm/kg by 1 year of age. Even in preterm infants born at 30–35 weeks' gestation, DDAVP administration can produce urine of >500 mOsm/kg by 4–6 weeks of age, although some infants have been shown to do so within the first few days of water deprivation.

ACID–BASE REGULATION

The mature kidneys are capable of providing metabolic compensation for respiratory acidosis or alkalosis by modulating tubular excretion of H^+ (as NH_4^+ and other titrable acids) or increasing reabsorption of HCO_3^- (the predominant buffer in the extracellular fluid). Recent human data suggest that these compensatory mechanisms are not as immature as once assumed.

HCO_3^- is the predominant buffer in the extracellular fluid, is freely filtered in the glomerulus, and is reabsorbed almost completely throughout the length of the tubules. The proximal tubule has very low permeability to bicarbonate and chloride. Almost 80% of the filtered HCO_3^- is reabsorbed in the PCT, and about 10% in the TALH. The remaining 10% is absorbed via the distal tubules. As the HCO_3^- concentration in the tubules decreases, the concentration of Cl^- increases, producing a transepithelial chloride gradient and thereby favoring paracellular transport.[23] As much as 20% of the HCO_3^- is absorbed

passively from these paracellular pathways into the peritubular capillary network in mature kidneys, although this pathway is limited in neonates due to the low paracellular permeability for bicarbonate.

The mechanism of HCO_3^- reabsorption across the tubule is similar. At the level of the PCT, H^+ in the lumen combines with HCO_3^- to produce carbonic acid (H_2CO_3), which further dissociates into H_2O and CO_2 in the presence of carbonic anhydrase IV; the latter is absorbed by the AQP-1 gas channels. Once CO_2 is within the cell, carbonic anhydrase isoenzyme II converts CO_2 and H_2O back to H_2CO_3 to regenerate H^+ and HCO_3^-. HCO_3^- is transported across the basolateral membrane by the NBCe-1A (Na^+-$3HCO_3^-$) cotransporter in the proximal tubules and by the Cl^- exchanger (Cl^- HCO_3^-, AE1) in the collecting duct.[68] When secretion of H^+ in response to HCO_3^- reabsorption in the distal tubules results in an acidic pH below 6.4, additional H^+ excretion occurs as NH_4^+ and NaH_2PO_4 and is increased by aldosterone. Sodium and potassium concentrations, angiotensin II, PTH, and the extracellular fluid (ECF) status all affect tubular H^+ secretion. The ability of preterm infants born at 29 weeks to respond to an acid load is not fully developed until 3 weeks after birth.

The reabsorption of HCO_3^- is accompanied by equimolar secretion of H^+ into the tubular lumen by the NHE pump (NHE isoforms NHE-3 and NHE-2), which has a third of the activity rate of adults.[23] The secretion of H^+ in turn is regulated by the active extrusion of Na^+ from the basolateral membrane by the Na^+ K^+ ATPase to maintain a concentration gradient for Na^+. In addition, a vacuolar H^+ ATPase pump on the apical membrane contributes nearly one-third of the H^+ secretion in the proximal tubules.

In the distal tubules (collecting ducts), the secretion of H^+ facilitates HCO_3^- reabsorption by the intercalated cells. In the α-intercalated cells, H^+ ATPase and H^+ K^+ ATPase pumps on the apical membrane regulate H^+ secretion; the β-intercalated cells present in the cortical collecting duct, secrete HCO_3^- for Cl^- at the apical membrane (via the solute-linked carrier 26 [SLC26] isoforms),[69,70] and then extrude H^+ across the basolateral membrane via the H^+ ATPase pump.

Preterm infants have lower serum bicarbonate levels (16–20 mEq/L) than term infants (19–21 mEq/L) and adults (24–28 mEq/L) due to a lower renal threshold for HCO_3^-. The primary determinant of renal HCO_3^- threshold in preterm infants is the extracellular fluid status, not prematurity per se or the intrinsic tubular reabsorption capacity. When a HCO_3^- load is given in the presence of extracellular volume contraction, the HCO_3^- threshold and tubular reabsorption of HCO_3^- increase, thereby making the urine more acidic, and vice versa.[71] The limited reabsorption of bicarbonate in neonates is secondary to the limited activity of the NHE pump and active transport rather than passive back leak.[23] The increase in expression of NHE isoform with maturation (and with steroids and thyroid hormone) likely explains the higher plasma bicarbonate levels seen in more mature infants. Further, the absence of carbonic anhydrase isoenzymes limits the ability for HCO_3^- reabsorption in the proximal tubules, resulting in an increased delivery of HCO_3^- to the distal tubules, as seen with proximal renal tubular acidosis (RTA).

Urinary loss of bicarbonate in preterm infants persists until the readjustment of the ECF and maturation of the carbonic anhydrase system in the proximal tubules. The carbonic anhydrase system is functional by 24–26 weeks in the juxtamedullary nephrons, but not in the cortical nephrons until nephrogenesis is complete, by 34–36 weeks, and is at levels similar to those of adults at term. Clinically, the more immature infants show persistent metabolic acidosis that usually resolves by 2 weeks after birth. In animal models as well, postnatal maturation of the carbonic anhydrase system is enhanced by glucocorticoids and correlates with an increase in the tubular absorptive surface area and maturation of the NHE cotransporters. However, in humans, the role of glucocorticoids in this regard is not as well described.

Inherited forms of proximal RTA have been described with genetic mutations in the NBC-1 cotransporter (also known as solute-linked carrier SLC4A4), carbonic anhydrase II, and pyruvate carboxylase deficiency. Distal RTA has been described with mutations in AE1 (autosomal dominant) and the vacuolar H^+ ATPase (also called the ATP6V1-B1 subunit, autosomal recessive with sensorineural hearing loss) genes.

The kidneys also maintain acid–base homeostasis by excreting acid predominantly as ammonia. H^+ generated in the form of volatile (H_2CO_3_ excreted by lungs as CO_2) and fixed acids is initially buffered by HCO_3^- before being excreted predominantly as ammonium (NH_4^+). NH_3 is generated from glutamine in the proximal tubules, and both NH_3 and NH_4^+ are secreted into the lumen, mostly via the NHE-3 transporter (upregulated by metabolic acidosis), as well as NHE-3-independent channels.[72] The TALH reabsorbs the majority of luminal ammonia via the apical Na-K-2Cl transporter, resulting in an increase in medullary interstitial NH_3 concentrations. NH_3 diffuses into the collecting duct lumen, where it is buffered again to generate NH_4^+, which is then excreted in the urine. However, while acid excretion in the fetus is carried out by the placenta, tubular mechanisms for excreting an acid load are functional in the third trimester and newborn infants are able to excrete an acid load. The other titrable acid, NaH_2PO_4 generated from Na_2HPO_4, is also functional in newborn infants.

EFFECTS OF PRETERM BIRTH AND OLIGONEPHRONIA

Preterm kidneys with fewer functional nephrons have been linked to hypertension and renal dysfunction in adults despite data to suggest that renal growth occurs to compensate for reduced nephron mass at birth.[73]

Since nephrogenesis is not complete until 34–36 weeks' GA, it is also important to understand the effects on renal growth following birth at an earlier gestation, as the majority of nephrons are formed late in gestation. A decrease in radial glomerular counts and glomerular generations was noted in autopsy specimens of preterm compared with term infants.[74] Other studies have also shown that renal growth does not follow the same intrauterine patterns as growth following preterm birth. In a baboon

model, Sutherland et al. noted that although nephrogenesis continued following preterm birth, postnatal glomerular growth was likely to be abnormal.[75] In another study,[76] Sutherland et al. compared renal growth in postnatal autopsy specimens following preterm delivery and in gestational-matched fetal deaths. They noted accelerated renal maturation after preterm birth, with an increased number of glomerular generations (also correlated with body weight and kidney weight), a decreased width of nephrogenic zones, and more immature glomeruli, particularly in the outer cortex. The percentage of glomeruli in the immature stages also decreased with increasing postconceptional age. Of importance, compared with gestational-matched control, preterm kidneys had a greater percentage of morphologically abnormal glomeruli and a significantly larger cross-sectional area of the renal corpuscle, suggestive of renal hyperfiltration.[76]

In other conditions associated with loss of nephron mass, such as outflow track obstruction or multicystic dysplastic kidney resulting in nonfunctioning kidney early in gestation, there is a significant increase in the size and weight of the contralateral kidney, with adequate renal function suggesting that the single-nephron GFR is increased. However, the hyperfiltration has been linked with focal glomerular sclerosis and renal failure in adulthood. Intrauterine growth restriction (IUGR), due to either maternal, placental, or fetal reasons, results in a decrease in the number of nephrons at birth.[77,78] Low birth weight is also associated with a decrease in the number and volume of glomeruli at birth.[79,80] Maternal nutritional status and specific nutrient deficiencies (vitamin A), smoking and alcohol, and fetal exposure to medications such as ACE inhibitors and PGE inhibitors, steroids, and aminoglycosides have all been linked with a decrease in the number of glomeruli at birth.[81] The timing of nephron loss during development may affect later adaptation. For example, unilateral nephrectomy in neonatal but not adult rats impairs RBF autoregulation and salt-sensitive hypertension in adulthood.

SUMMARY

The fetal kidneys produce urine by modifying blood ultrafiltrate at the level of the glomerulus into urine by reabsorption and secretion of solutes. The fetal kidneys are fully functional in utero, although they are limited in their concentrating capacity and in their ability to fully excrete a solute load. Nephrogenesis is completed by 34–36 weeks' GA, and postnatal renal growth after this age occurs secondary to an increase in existing glomerular and tubule size, not number. Following preterm birth, functional maturation occurs within a few weeks irrespective of the severity of preterm birth.

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CHAPTER 23

Cystic Kidney Disease

Roshan P. George and Larry A. Greenbaum

INTRODUCTION

Cyst formation is seen in a variety of kidney diseases (Table 23.1). Many of these diseases are genetically inherited, and many are associated with extrarenal manifestations. They are generally rare diseases, although a few are common enough to cause considerable pediatric morbidity and mortality. Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common human genetic diseases, but its manifestations are usually fairly subtle in pediatric patients. It does cause considerable morbidity for adults, and it is likely that future therapy of this disease will focus on the pediatric patient.

The last decades have witnessed considerable advances in our understanding of cystic kidney diseases. The defective gene or genes have been cloned in many of these diseases, and this has led to increased understanding of pathogenesis and clarified some important clinical issues. Such genetic studies have also provided opportunities for improved prenatal and postnatal diagnoses.

Identification of genes and proteins that are defective in the inherited cystic diseases has led to the discovery that most of these proteins are expressed in the primary cilium of renal epithelial cells.[1–3] Primary cilia are nonmotile sensory organelles that detect extracellular stimuli and are highly conserved through evolution.[4] Primary cilia have a crucial role in modulating differentiation, migration, and proliferation of tubular epithelium. Current evidence suggests that there may be a common pathway for cyst formation, potentially related to the role of primary cilia in signal transduction.[5,6] This has led to the designation of "ciliopathies" for this group of disorders.[7]

AUTOSOMAL RECESSIVE POLYCYSTIC KIDNEY DISEASE

The incidence of autosomal recessive polycystic kidney disease (ARPKD) has been estimated to be from 1 in 6,000 to 1 in 55,000.[8,9] The true incidence may be higher due to undiagnosed fatal neonatal disease.[10] Since ADPKD can present in infancy and ARPKD can present in young adults, the designation ARPKD is more precise than the term *infantile polycystic kidney disease*. Both the liver and kidneys are affected in ARPKD, with significant variability in severity between patients. Clinically, the prognosis for patients with ARPKD continues to improve.

Genetics

ARPKD is a classic recessively inherited disorder, with unaffected heterozygote parents and a 25% risk of an affected child in subsequent pregnancies. All cases of ARPKD are due to a mutation in the polycystic kidney and hepatic disease 1 (*PKHD1*) gene, located on chromosome 6, which encodes the protein fibrocystin (also called polyductin).[11,12] Fibrocystin has been identified in the collecting duct and the thick ascending limb of the kidney and in the epithelial cells of the hepatic bile duct, expressed in the primary apical cilia.[2,13] There is a correlation between the type of mutation and the clinical presentation. Infants with two truncating mutations typically die as neonates, while the clinical presentation varies in children with at least one missense mutation.[14,15] The severity of ARPKD is usually similar among children within the same family, but there are examples of families where siblings have very different clinical manifestations.[15–18]

Pathology

The kidneys are enlarged bilaterally. This enlargement is usually fairly symmetrical, and the kidneys retain their reniform shape. Careful examination of the kidney capsule will often reveal opalescent dots, which are due to the termini of dilated collecting ducts below the kidney capsule (Figure 23.1). Grossly, the kidneys have a spongy appearance because of the cystic dilations of the collecting ducts.[19] Large cysts are unusual in infancy, although there is a gradual increase in cyst size over time.[20] The microscopic appearance is dominated by the dilated collecting ducts, which are perpendicular to the kidney surface (Figure 23.2). The cysts are lined with a normal-appearing single layer of cuboidal or columnar epithelium.[19] The glomeruli often appear normal in newborns. Over time, there is increased interstitial fibrosis and glomerular sclerosis.

These patients have the typical features of congenital hepatic fibrosis.[21] There is proliferation and dilation of bile ducts and fibrosis of portal tracts. The distal portal veins are small, providing a microscopic explanation for the presence of portal hypertension. The absence of hepatocyte destruction correlates with the preservation of liver function in most patients.[22]

TABLE 23.1 Cystic kidney diseases

Polycystic kidney disease
Autosomal recessive polycystic kidney disease
Autosomal dominant polycystic kidney disease
Cysts of the medulla
Juvenile nephronophthisis
Medullary cystic disease
Medullary sponge kidney
Glomerulocystic kidney disease
Sporadic glomerulocystic kidney disease
Familial hypoplastic glomerulocystic kidney disease
Autosomal dominant glomerulocystic kidney disease
Multicystic dysplasia
Simple renal cysts
Multilocular cysts
Acquired cystic kidney disease
Syndromes with cystic kidneys
Tuberous sclerosis
Meckel syndrome
von Hippel–Lindau disease

Clinical Features

There is significant variability in the clinical features of ARPKD (Table 23.2). Antenatal ultrasound, demonstrating hyperechogenic, markedly enlarged kidneys with no identifiable cysts, can detect ARPKD by 24 weeks of gestation.[23] The majority of patients present during the first year of life, with a significant percentage presenting during the first month of life.[20,24–26] The most severely affected neonates can have some degree of Potter syndrome due to oligohydramnios. Along with abnormal facies and joint deformities, these children have respiratory compromise due to pulmonary hypoplasia. Volume overload from renal failure and poor diaphragm function secondary to the enlarged kidneys can also impair respiratory function. Respiratory failure is thus fairly common in neonates.[20,24–26] The importance of the mass effect of the enlarged kidneys has been confirmed by demonstrating improvement in respiratory function following unilateral nephrectomy.[27] Pneumothoraces are probably related to the hypoplasia and the high ventilatory settings that these infants require. Death due to respiratory failure can occur in the first few days of life.[24]

The kidneys in ARPKD are typically large at birth and often increase in size. This causes abdominal distention on physical examination, but also has additional important secondary consequences. By limiting diaphragm mobility, respiratory function is compromised, adding to the problems described above. In addition, the enlarged

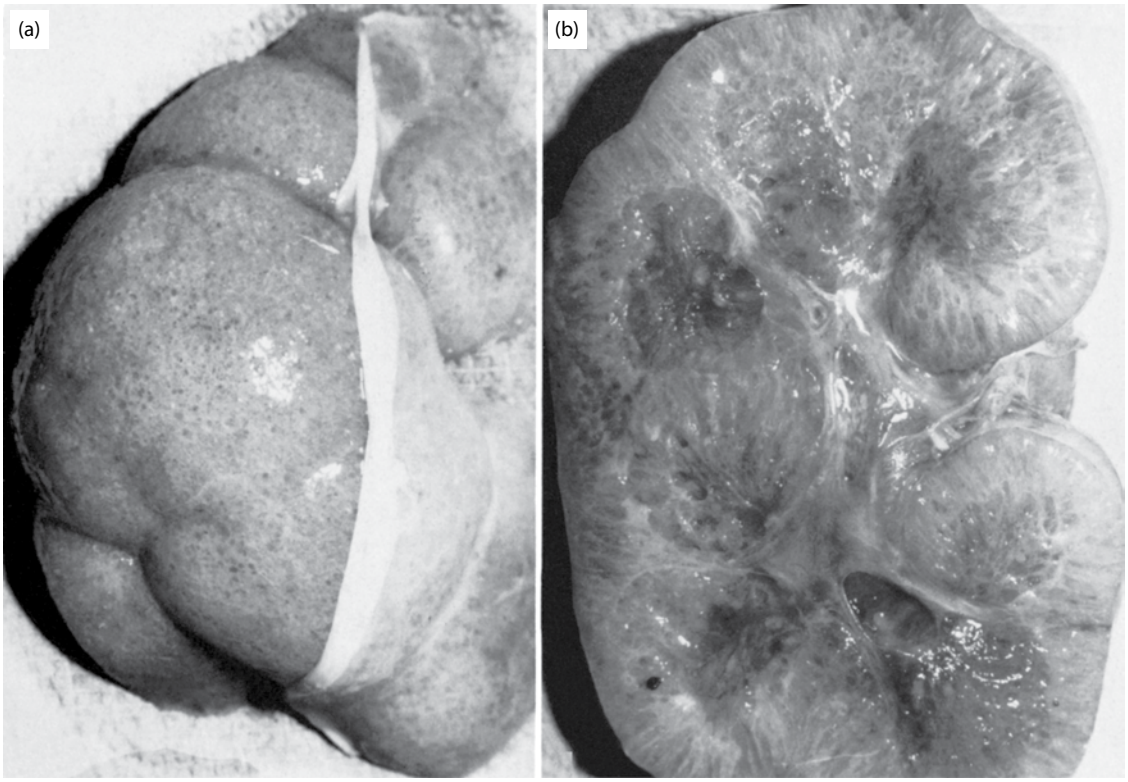

FIGURE 23.1 (a) Subcapsular surface of an ARPKD from a neonate. Innumerable small cysts can be seen beneath the capsule. (b) Cross section of the same kidney. The radial arrangement of the dilated ducts can be seen.

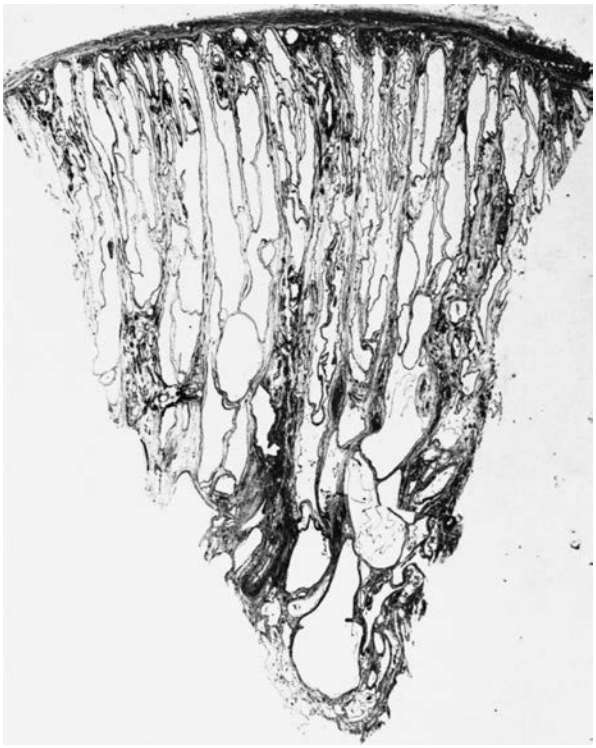

FIGURE 23.2 Low-power view of the cortex from an ARPKD. Notice the arrangement of dilated ducts, which are perpendicularly oriented to the capsule. Hematoxylin and eosin, ×8.

kidneys may impair gastric feeding[27] and patient mobility. It is important to note, however, that the kidney size can become less impressive over time in some patients, especially those who are receiving chronic dialysis.[20,28]

Chronic kidney disease and, ultimately, end-stage renal disease (ESRD) is the usual outcome in ARPKD. ESRD may be present at birth,[20,26] although it more typically develops gradually, with most children who survive the neonatal period not progressing to ESRD until later in childhood or even as young adults.[28,29] Many patients have some improvement in renal function during the first year of life, followed by a period of stabilization and subsequent decline.[30,31] This is probably secondary to the normal maturation of kidney function. More aggressive therapy in the newborn period might theoretically select for patients with more severe renal involvement, although neonatal presentation is not necessarily a marker for earlier progression to ESRD.[28]

TABLE 23.2 Presenting complaints in ARPKD

Respiratory distress
Enlarged kidneys
Renal failure
Abnormal prenatal ultrasound
Hypertension
Pyuria
Proteinuria
Failure to thrive
Disease in a sibling
Hepatomegaly
Esophageal varices

Chronic kidney disease, especially untreated, is a potential cause of growth retardation. In addition, poor food intake, due to both renal failure and abdominal distention, may cause malnutrition. Not surprisingly, growth retardation is quite common in ARPKD,[20,32] and some children have severe growth retardation without a clear etiology.[28]

Hypertension is very common, probably due to fluid overload. This may be secondary to activation of the local renin–angiotensin system and increased sodium retention,[33] although two studies failed to demonstrate increased systemic renin or aldosterone levels.[24,28] Anywhere from 65% to 78% of patients require antihypertensive therapy.[9,24,26,28,31] The hypertension can be quite severe, causing severe morbidity[34] and even death.[24,28] Hypertension gradually diminishes in some children, and this may permit weaning of antihypertensive medications.[28]

There is an increased incidence of urinary tract infections (UTIs);[9,26,35] this may be related to vesicoureteral reflux (VUR) and catheterization,[36] and is more common in girls.[32,35] However, pyuria is often present in the absence of infection;[20] it appears to be less common in older children.[28] Proteinuria may be detected, often intermittently,[26,37] but it is not of sufficient magnitude to cause clinical problems. Gross hematuria is uncommon, but has been reported.[28]

Patients can have the typical electrolyte disturbances associated with renal failure, such as hyperkalemia and hyperphosphatemia. Acidosis develops with significant renal failure, but may be present earlier due to impairment in tubular acid excretion.[28,38] Patients almost always have a decreased ability to concentrate their urine,[26,28,38] and thus are at risk for dehydration and nocturnal enuresis. There is an increased risk of hyponatremia, which is most common in infants.[24,35]

Portal hypertension due to congenital hepatic fibrosis leads to a number of complications. The liver may be enlarged and spider nevi are sometimes visible.[26,28,32,36,39] Splenomegaly was present in 47% of patients over 3 months of age in one series,[24] and this increased to 60% in children over 1 year of age.[36] This can be associated with anemia and thrombocytopenia.[36,39] Esophageal varices can lead to problems with hematemesis;[39,40] variceal rupture can be fatal.[24,26,36] Dilated biliary ducts predispose children with ARPKD to develop cholangitis.[35,39] This can occur in the neonatal period, and it has been fatal in some children.[26] Hepatocyte damage does not occur, and synthetic function remains normal,[39,40] although mild abnormalities in liver enzymes are occasionally detected.[26,32] Overall, approximately 7% of patients surviving the neonatal period will eventually need liver transplantation for complications resulting from cholangitis and portal hypertension.[35]

Some patients initially have predominant liver involvement,[9,39] with kidney abnormalities discovered as an incidental radiographic finding. In fact, there are some adults

diagnosed with congenital hepatic fibrosis or Caroli's disease who have mutations in the *PKHD1* gene.[41] Other children have both severe liver and kidney disease at an early age.[28] A single-center retrospective review, looking at 133 patients between 1961 and 2004, indicated that patients diagnosed in infancy were more likely to have renal manifestations and secondary pulmonary insufficiency than patients presenting later in life, who showed more hepatic manifestations.[10] The hypothesis that severe liver disease predicts minimal renal involvement[42] is no longer accepted.[21]

It is possible that additional clinical features of ARPKD may be discovered as patients survive further into adulthood. For example, intracranial aneurysms were described in a 31-year-old patient with ARPKD.[43] While only a case report, this is especially intriguing given the presence of intracranial aneurysms in ADPKD.[44]

Radiologic Features

Intravenous pyelogram (IVP) shows enlarged kidneys with a delayed nephrogram (Figure 23.3).[45,46] Radial streaks due to contrast in the dilated collecting ducts are usually present in infancy, but may not be visible in older children.[25] Because of concerns regarding intravenous contrast, a renal ultrasound is now the usual frontline diagnostic test. Ultrasound shows enlarged kidneys with increased echogenicity and poor corticomedullary differentiation (Figure 23.4);[47,48] a hypoechoic rim is often visible.[49] Older children have increased medullary echogenicity, which may resemble nephrocalcinosis.[28] Reversal of corticomedullary differentiation has been reported; it is an important finding, as few other conditions cause reversed corticomedullary differentiation.[50] Multiple small cysts may be visible by ultrasound,[28,48] but this is quite variable (Figure 23.5). Macrocysts are sometimes visible in older children.[43,47,48,51]

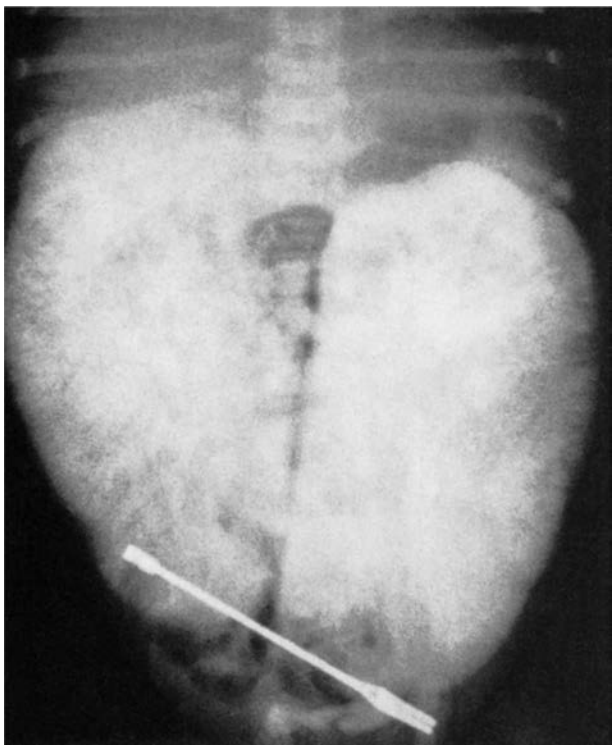

FIGURE 23.3 IVP from a 2-day-old girl with ARPKD. Notice the sunray appearance of the contrast material and the enormous renal size.

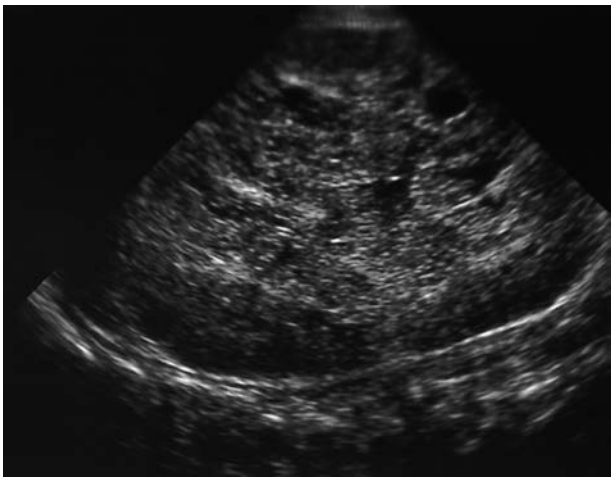

FIGURE 23.4 Renal ultrasound of a newborn with ARPKD. The kidney is enlarged, with increased echogenicity. A hypoechoic rim is visible. (Courtesy of Dr. J. Sty, Children's Hospital of Wisconsin, Milwaukee.)

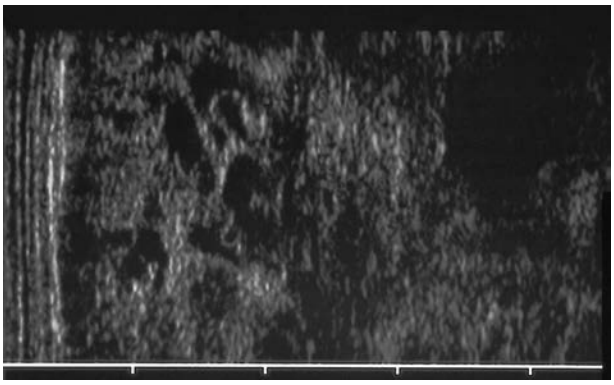

FIGURE 23.5 High-resolution renal ultrasound of the same patient shown in Figure 23.4. High-resolution cysts are seen, and the hypoechoic rim is still visible. (Courtesy of Dr. J. Sty, Children's Hospital of Wisconsin, Milwaukee.)

Ultrasound detects liver abnormalities in approximately 50% of patients.[28,35] It is often possible to detect dilations of the peripheral intrahepatic biliary ducts and the principal biliary duct. There may also be evidence of portal hypertension.[28] Magnetic resonance imaging (MRI) and computed tomography (CT) may provide better visualization of renal and hepatic findings in the setting of equivocal ultrasound results.[52]

Diagnosis

A large percentage of children are now diagnosed due to an abnormal prenatal ultrasound.[35] The presence of bilaterally enlarged kidneys during the first few years of life is suggestive of ARPKD. The radiologic features, as detailed above, can be helpful, but are not always conclusive. This

is especially true in older patients with ARPKD since cysts may be enlarged and thus resemble those seen in ADPKD.[43] It is important to investigate the family history; the presence of a sibling with ARPKD is obviously highly suggestive. Consideration must be given to an early presentation of ADPKD, and therefore it is now common to augment the family history with renal ultrasounds of the parents, and possibly the grandparents if the parents are young, to rule out this possibility. In one study, 6.7% of the patients with neonatally lethal polycystic kidney disease had ADPKD.[26] For inconclusive cases, histological examination of the liver is useful. Congenital hepatic fibrosis is always present in ARPKD and is extremely rare in ADPKD.[53,54] Liver ultrasound may also demonstrate hepatic disease.[28] Kidney biopsy is rarely performed because of concerns regarding the safety of the procedure in these children. In the histological evaluation of the kidney, the absence of glomerular cysts supports a diagnosis of ARPKD.

Genetic diagnosis is commercially available, but challenging because the *PKDH1* gene is extremely large and complex and the known mutations are quite heterogeneous.[15,41] Mutations are more likely to be detected in children with severe ARPKD than in children with moderate disease.[15,41]

Nephroblastomatosis and bilateral Wilms' tumor are part of the differential diagnosis of bilaterally enlarged kidneys. Transient nephromegaly of the newborn can be confused with ARPKD,[55] but this resolves relatively quickly. A variety of other diseases with renal involvement can also have hepatic manifestations. These include Meckel syndrome,[56] juvenile nephronophthisis (NPHP),[57] Ivemark syndrome,[58] Jeune syndrome,[59] COACH syndrome,[60] and Bardet–Biedl syndrome.[61]

Prenatal Diagnosis

Prenatal ultrasound often detects abnormalities in a fetus with ARPKD.[9,23,62–66] The kidneys may be hyperechoic[63] and increased in size.[64–66] Serial ultrasound showing inappropriate increases in kidney length improves diagnostic reliability.[23] In addition, some fetuses have oligohydramnios. However, a precise diagnosis is often impossible prenatally given the limits of current imaging and alternative diagnostic possibilities. Naturally, in a family with a previous child who has ARPKD, the clinical likelihood of this diagnosis is increased. Unfortunately, there have been cases of both false-positive and false-negative diagnoses.[63,67] False positives are especially likely in a fetus without a family history of ARPKD or if oligohydramnios is not present.[63] Conversely, in a family at risk, a normal prenatal ultrasound, especially before the third trimester, should not be used to predict an unaffected child.[18,66–68] Fetal MRI has also been used to diagnose ARPKD.[69]

As stated previously, mutation screening is difficult and not 100% sensitive.[15,41,70] Linkage analysis can determine if a fetus has ARPKD in families with a previous affected child.[71] This analysis requires preservation of DNA from the previous child. The clinical course of a previously affected child does not always predict the severity of the ARPKD in a subsequent child.[18,24] Parents clearly need genetic counseling regarding this possibility. Supplementing linkage analysis with prenatal imaging studies could theoretically aid in this discussion, but it is especially difficult to make outcome predictions based on the fetal ultrasound.[18]

Treatment

The initial management of respiratory distress is quite challenging. In the past, many of these children were presumed to have pulmonary hypoplasia, and thus therapy was limited. It is now clear that other factors contribute to the respiratory insufficiency. Both unilateral and bilateral nephrectomies, by decreasing the effect of abdominal distention, have been successfully used to improve respiratory function and allow children to wean from respiratory support.[27,72] Although providing a less dramatic decrease in abdominal distention, unilateral nephrectomy can be done without forcing the patient to undergo dialysis.[27] It is important to evaluate relative renal function before proceeding with a unilateral nephrectomy, lest the remaining kidney have limited function. Bilateral nephrectomies require that a peritoneal dialysis catheter be placed simultaneously; it is therefore recommended that the kidneys be removed extraperitoneally, with meticulous attention to the peritoneal membrane.[72]

Reversible causes of respiratory insufficiency, such as volume overload, persistent fetal circulation, hyaline membrane disease, infection, and pneumothoraces, should be treated before concluding that a patient has irreversible pulmonary failure. The use of more aggressive perinatal support strategies, such as surfactant, high-frequency oscillatory ventilation,[27] extracorporeal membrane oxygenation (ECMO), dialysis, and hemofiltration, may also decrease the mortality from respiratory failure.

The massively enlarged kidneys create a variety of problems beyond respiratory distress. Both unilateral and bilateral nephrectomies can have other benefits, such as improved tolerance of feedings[27] and increased activity in older children. Left nephrectomy, assuming equivalent renal size, may have more benefits for gastric function than a right nephrectomy.[27]

Hypertension should be aggressively treated, given that uncontrolled hypertension has been associated with severe complications and even death.[24] Hypertension frequently requires multiple medications,[35] and is often difficult to control,[9] leading to bilateral nephrectomy and the initiation of peritoneal dialysis in some children.[36] Interestingly, hypertension may sometimes lessen as the patient ages, allowing successful weaning of antihypertensive medications.[31,36]

Chronic kidney disease and ESRD are managed using the usual strategies. Patients are treated for electrolyte problems, anemia, and renal osteodystrophy. Tube feedings and growth hormone are often necessary to manage failure to thrive. Dialysis and, ultimately, transplantation are needed when the patient reaches ESRD. Both peritoneal dialysis and transplantation often require prior nephrectomies to create sufficient abdominal space.

Complications of portal hypertension need to be addressed.[73] Esophageal varices may require sclerotherapy or placement of a portacaval shunt,[39,74] with one patient receiving a shunt as early as 2 years of age.[24] Cholangitis

needs to be aggressively treated with antibiotics. Splenectomy has been performed in children with intractable hypersplenism that causes anemia and thrombocytopenia.[36] Liver transplantation is occasionally necessary.[35] Hepatic complications can cause significant morbidity and mortality after renal transplantation.[75]

Prognosis

ARPKD is associated with considerable morbidity and mortality. Improved therapy in the newborn intensive care unit and better treatment for chronic kidney disease is continually changing the long-term prognosis. Nevertheless, patients continue to die, with much of the mortality occurring in the first year of life, especially during the first month.[24,26,28,35] Respiratory failure and sepsis are currently the most common causes of death.[35] Neonatal ventilation is a strong predictor of mortality and the early development of chronic kidney disease.[35] Children who survive beyond the first month had a 5-year survival of 87% in a report of a North American registry.[35]

There is clearly significant long-term morbidity in these patients due to chronic kidney disease, systemic hypertension, and portal hypertension. However, patients are continuing to benefit from improvements in surgical and medical management.

AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

ADPKD, with an incidence of 1:400 to 1:1000, is the most common inherited kidney disease. Although kidney involvement, with cystic dilation in all parts of the nephron, is the major feature for most patients, there are protean extrarenal manifestations, including the potentially life-threatening possibility of a ruptured intracranial aneurysm. Severity varies greatly between patients, and symptoms tend to develop over time. Fortunately, most children are asymptomatic; even middle-age adults may be unaware of their diagnosis. There are, however, some ADPKD patients who present with severe neonatal disease, which can have significant morbidity and can occasionally be fatal.[30] This underscores the importance of avoiding the term *adult polycystic kidney disease*.

An increasing percentage of children with ADPKD are diagnosed due to a positive family history or because of an incidental finding during an imaging study. This has caused a marked shift in the pediatric patient population, with many patients having no symptoms and requiring very limited intervention.

Genetics

ADPKD is a genetically heterogenous condition; disease occurs due to mutations in one of two genetic loci (Table 23.3). Patients with a mutation of the *PKD1* gene,[76] which is located on chromosome 16, account for the majority of cases. Most remaining cases are due to a mutation in the *PKD2* gene on chromosome 4.[77] While initial studies suggested that 15% of cases are due to *PKD2* mutations, it now appears that *PKD2* mutations cause a higher percentage of cases.[78]

TABLE 23.3 Gene defects causing ADPKD

Gene	Chromosome location	Protein
PKD1	16p	Polycystin
PKD2	4q	Polycystin 2

PKD1 encodes for a protein called polycystin 1, which is a transmembrane protein with multiple extracellular domains.[79] The *PKD2* gene product, polycystin 2, is also a transmembrane protein and has moderate homology to polycystin 1.[77] Polycystin 2 is a calcium-permeable, nonselective, cation channel that increases calcium permeability of the cell membrane.[80] Polycystin 1 and polycystin 2 interact with each other, and are localized within primary cilia.[81–83]

The variable development of cyst formation in ADPKD appears to be related to the need for a second inactivating mutation. The kidney cells of patients with the *PKD1* mutation initially have one normal allele for polycystin and one defective gene. Cyst formation occurs when there is a second somatic mutation that inactivates the normal gene. This produces a cell that does not produce any normal polycystin. Additional cysts are due to a second mutation in other cells.[84,85] A similar mechanism takes place in patients with *PKD2*.[86,87] This helps to explain why cysts appear fairly randomly and increase in number over time.

There is a great deal of variability in the severity of ADPKD. It is clear that some of this variability is based on the specific gene affected. Patients with *PKD2* have less severe symptoms, including later mean age for the development of ESRD and a decreased incidence of hypertension, UTIs, and hematuria.[88,89] In one study, the median age of death or onset of ESRD was 53 and 69 years in patients with *PKD1* and *PKD2*, respectively.[88] This difference in severity has been shown to be due to cysts forming earlier in *PKD1* patients; the rate of cyst growth, once formed, is similar in *PKD1* and *PKD2* patients.[90]

There is also evidence that the disease severity is influenced by the specific mutation (allelic heterogeneity) in the *PKD1* or *PKD2* genes.[91–93] Additional sources of variability may involve environmental factors and genetic differences at other loci.[94–96] For example, polymorphisms in the angiotensin-converting enzyme (ACE) gene modify renal disease severity in patients with *PKD1*.[97] In cases of neonatal ADPKD, the affected parents have not had early-onset disease.[26,98,99] However, there appears to be an increased likelihood of early disease in affected siblings[26,98,100,101] and other members of the same kindred.[99] Early-onset disease may be more likely in families with mutations in *PKD1*.[102]

Pathophysiology

The kidneys are typically enlarged and have random cysts, which can originate from any portion of the nephron (Figure 23.6). Except for cysts, the renal architecture is initially normal, although as the disease progresses, fibrosis and glomerulosclerosis gradually increase.

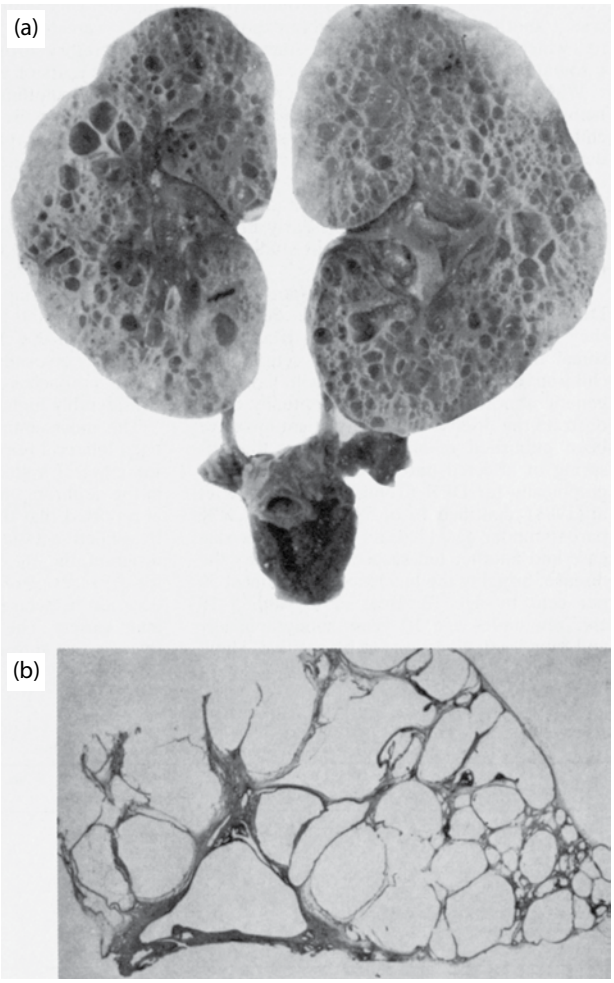

FIGURE 23.6 (a) Example of adult polycystic kidney disease in a 3-month-old. Notice the rounded cysts of varying size. (b) Low-power view of the same kidney. Foci of normal renal tissue are seen between the grossly dilated tubules. (Reproduced from Blyth H, Ockenden BG. *J Med Genet* 1971;8:257–84. With permission.)

In ADPKD, there is dysfunction of the primary cilia; it is a ciliopathy. Cilia are essential in maintaining cell polarity, a process that is important during cell division and proliferation.[103] Primary cilia are mechanosensors, converting mechanical signals such as fluid flow into a chemical signal within the cells, and are also involved in signal transduction of paracrine signals, such as Wnt, Sonic Hedgehog (Shh), and platelet-derived growth factor α.[103–106] In rodent models, the noncanonical Wnt and planar cell polarity signaling are important for the regulation of cell polarity during the development of the renal tubules. In ADPKD, there is abnormal signaling by the primary, and this causes misorientation of the mitotic spindle in relation to the longitudinal axis of the tubule, resulting in the formation of cysts.[107]

Cyclic adenosine monophosphate (cAMP) is a second messenger for multiple signaling pathways, and increased cAMP occurs in human ADPKD and animal models of polycystic kidney disease.[108] The V2 receptor (V2R), when activated, produces cAMP. In several animal models of cystic kidney disease, there is increased V2R activity and V2R antagonists slow cyst progression.[109] Other pathways and receptors implicated in the pathogenesis of cyst development include the epidermal growth factor family and its related receptors and the mammalian target of rapamycin (mTOR) pathway.[110–112]

Clinical Features

Most children with ADPKD are asymptomatic, and increasing numbers of these patients are diagnosed based on a positive family history, followed by a screening CT scan or ultrasound. Others are diagnosed after kidney cysts are incidentally noted on an imaging study, including prenatal ultrasound.

Although children are often asymptomatic, there are reports of severe disease, including neonatally lethal disease.[26,98,113] Neonatal mortality is usually due to respiratory failure and is associated with massively enlarged kidneys.[26,100,113] Most neonates diagnosed based on an abnormal prenatal ultrasound are asymptomatic. The majority of these children maintain normal renal function, but some will reach ESRD during childhood.[28,102,113,114] Maternal inheritance may be a risk factor for neonatal presentation.[115]

Most children with symptomatic ADPKD have a more subtle presenting complaint, typically in late childhood or adolescence.[26,28] Hematuria is quite common in adults with ADPKD[116] and can manifest in childhood.[26,28,117,118] Other presenting symptoms include hypertension, frequency, abdominal or flank pain, abdominal mass, UTI, and proteinuria (Table 23.4).[26,28,118,119] The majority of patients who are symptomatic during childhood do not have renal insufficiency as young adults,[28] but they may be at a higher risk for early kidney failure.[118]

The presence of symptoms in children correlates with the number of cysts. Children with more than 10 cysts have an increased incidence of flank or back pain, palpable kidneys, and hypertension.[119] Such children also have more complaints of palpitations and urinary frequency than their unaffected siblings.[119]

Hypertension and resultant end-organ damage occurs at an earlier age in children with ADPKD than in their healthy peers.[120] When a group of mostly asymptomatic children were screened, 13% had hypertension (vs. 0% of controls) and the hypertensive patients had left ventricular

TABLE 23.4 Presenting complaints in symptomatic children with ADPKD[a]

References	Gagnadoux et al.[28]	Fick et al.[119]	Kääriäinen et al.[26]
Hematuria	3	2	2
Abdominal pain	3	1	1
Hypertension	3	1	0
Renal mass	1	1	0
Frequency	0	2	0
UTI	0	1	1
Proteinuria	0	0	1

[a] This table excludes patients with severe neonatal disease.

hypertrophy.[121] A smaller study using ambulatory blood pressure monitoring found no evidence of hypertension in patients below 15 years, but there was an increase in left ventricular mass.[122] In addition, patients between 15 and 25 years had significant increases in blood pressure and ventricular mass.[122] In another study, a significant proportion of normotensive young adults with ADPKD were found to be prehypertensive with blunted "nocturnal dipping" on ambulatory blood pressure monitoring.[123] Another study found hypertension at clinical presentation in 22% of children.[115] Not surprisingly, hypertension is more common in children who are symptomatic in the neonatal period.[26] The renin–angiotensin system is implicated in hypertensive adults with ADPKD and normal renal function,[124] along with reduced renal blood flow and sodium retention,[125] although these mechanisms have not been studied in children.

Some children with mild ADPKD have a subtle defect in urinary concentrating ability,[28] and this is more common in children with more than 10 cysts,[119] along with an increased incidence of proteinuria.[126] Kidney stones, often presenting as acute flank pain, are increased in adults,[127] but are infrequent in children.

Kidney infections are more common in patients with ADPKD, and complications may include perinephric abscess, septicemia, and death;[128] there may be an increased risk of VUR.[129] Cyst infection is especially troublesome since the urine culture may be negative and not all antibiotics achieve therapeutic levels in the cyst fluid.[128]

There are a large number of possible extrarenal manifestations in adults with ADPKD (Table 23.5). Extrarenal involvement is less common in childhood. Mitral valve prolapse (MVP) is found in 26% of adults with ADPKD.[130] Among a group of children, 12% had MVP (vs. 3% of controls), and the incidence increased with age.[121] Inguinal hernias are substantially increased in both children[118,119] and adults.[131,132]

TABLE 23.5 Extrarenal symptoms in ADPKD

Mitral valve prolapse
Hypertension
Extrarenal cysts
Hepatic cysts
Pancreatic cysts
Ovarian cysts
Testicular cysts
Arachnoid cysts
Splenic cysts
Pineal cysts
Seminal-vesicle cysts
Aortic aneurysms
Intracranial aneurysms
Hernias
Colonic diverticula
Cholangiocarcinoma
Congenital hepatic fibrosis

Liver cysts are the most common extrarenal manifestation in adults with ADPKD, with the prevalence increasing with age.[133,134] Women tend to have more and larger cysts;[135] pregnancy is an additional risk factor.[134] Some adults experience abdominal fullness and pain, but cysts almost never impair liver function or cause portal hypertension,[133,135] except in extreme cases.[136] Infected liver cysts present with pain, fever, and leukocytosis.[137] Liver cysts are rare in children,[119,138] but in a study of 230 patients between 15 and 46 years with ADPKD, MRI revealed an overall prevalence of hepatic cysts of 83%, and in the subgroup of patients from 15 to 24 years, the prevalence was 58%.[139] Liver enlargement[26] has occasionally been described in children.

Pancreatic cysts are present in only 9% of patients over 30 years of age,[140] and almost never cause complications;[141] they are extremely unusual in children.[138] The claim that ovarian cysts are increased in ADPKD has been questioned.[142] The remaining cystic complications are quite rare.[143]

Ruptured intracranial aneurysms are a significant cause of mortality in adults with ADPKD.[144] In one study, the mean age of bleeding was 39.5 years, but 10% of patients were less than 20 years.[145] There are reports of young children with a subarachnoid hemorrhage,[26] a bleeding arteriovenous malformation (AVM),[146] and ruptured intracranial aneurysms.[147,148] Aneurysms cluster in families,[149–151] and thus a positive family history for intracranial hemorrhage or aneurysm is an important risk factor.

Gender differences in ADPKD include the predisposition to liver cysts in women. The rate of progression to kidney failure is faster in adult males with either *PKD1*[152] or *PKD2*.[88] No gender differences among children have been reported.[119]

Radiologic Features

Ultrasound (Figure 23.7) and CT scan (Figure 23.8) are useful for detecting the macroscopic cysts of ADPKD. The number and size of cysts in children increase with age, and those children with more cysts have increased kidney size.[119] Increased renal echogenicity may be seen in some

FIGURE 23.7 Ultrasound of an infant with severe ADPKD. The kidneys are enlarged due to multiple cysts. (Courtesy of Dr. J. Sty, Children's Hospital of Wisconsin, Milwaukee.)

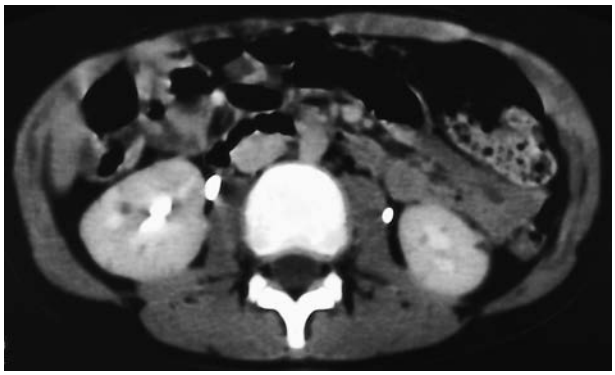

FIGURE 23.8 CT scan of a child with ADPKD. Macroscopic cysts are readily visible. (Courtesy of Dr. J. Sty, Children's Hospital of Wisconsin, Milwaukee.)

children.[48] Occasionally, children can have marked disease asymmetry, which can create diagnostic confusion.[153] Liver cysts are quite unusual in children.[119]

Diagnosis

Rare, early-onset ADPKD can sometimes be diagnosed by prenatal ultrasound,[98,99,154,155] although most cases are identified in the last 10 weeks of gestation. The kidneys are large, with increased echogenicity, and cannot easily be distinguished from the kidneys of children with ARPKD. Occasionally, macrocysts are identified.[154] Early diagnosis in a fetus with an affected parent is possible using DNA analysis.[156,157]

Even after birth, it is often difficult to distinguish early-onset ADPKD from ARPKD. Radiologic studies of the kidneys are often inconclusive. Liver imaging or biopsy is useful because hepatic fibrosis is always present in ARPKD. Kidney pathology is also helpful, given the absence of glomerular cysts in ARPKD. In ADPKD, cysts arise in every segment of the tubule and rapidly close off from its origin in the nephron. In ARPKD, by comparison, cysts are derived from the collecting tubule and remain connected to the nephron of origin. The presence of a parent with ADPKD is the most useful diagnostic clue. Yet, many parents are unaware of their own disease,[28,102] and thus screening imaging studies of "normal" parents are mandatory. Because of the possibility of a false-negative radiologic study, screening of the grandparents is sometimes useful, especially if the parents are less than 30 years old.

Diagnosis in asymptomatic or mildly symptomatic children is usually accomplished by renal ultrasound. The sensitivity and specificity of this approach increase with the child's age (Table 23.6). There are age-dependent ultrasound criteria for diagnosis.[158] It is important to note, however, that ultrasound cannot be used to exclude the diagnosis of ADPKD in asymptomatic patients younger than 40 years. Unilateral cysts may be the only initial finding in children with ADPKD,[28,119,147,153,159,160] and in the context of a positive family history, even a single cyst is highly suggestive of disease.[161] Bilateral cysts are frequently found on later investigation.[119] For adults, given the increased incidence of benign solitary cysts, more stringent criteria are necessary to avoid false positives.[162]

TABLE 23.6 Sensitivity and specificity of ultrasound for detecting ADPKD in children

Age	Specificity (%)	Sensitivity (%)
3 months–5 years	89	62
5 years–10 years	100	82
10 years–15 years	100	86
15 years–17.5 years	100	67

Source: Adapted from Gabow PA, Duley I, Johnson AM. *Am J Kidney Dis* 1992;20:140–3.

Note: This table summarizes the results of ultrasound screening in a group of children with *PKD1* by linkage analysis. The presence of a single cyst was interpreted as a positive ultrasound.

The ability to screen patients for mutations in the *PKD1* or *PKD2* genes is currently commercially available, although false-negative results can occur. Identifying a mutation in a known affected family member is useful for proving that a negative result is a true negative.

Treatment

A variety of interventions to slow the progression of ADPKD have been tested in animal models, and a phase III clinical trial of tolvaptan, a vasopressin 2 receptor antagonist, demonstrated a significantly slower increase in kidney volume than with placebo.[434] Tolvaptan has not been tested in children, and there is thus no recommendation to initiate tolvaptan in children. Moreover, since tolvaptan essentially causes nephrogenic diabetes insipidus, the massive polyuria may be a challenging side effect in children.

The mTOR inhibitor rapamycin was shown to stabilize cyst growth in a randomized crossover study (SIRENA) at 6 months,[163] but two larger randomized trials of mTOR inhibitors in adults with longer periods of follow-up did not show functional benefits with these agents.[164,165]

Children with severe disease receive standard therapy for chronic kidney disease. This should include careful monitoring of nutrition and growth. In adults with moderate renal insufficiency, there was no benefit to protein restriction, although there was a marginal slowing in the rate of glomerular filtration rate (GFR) decline in patients with severe renal insufficiency.[166] Such an approach is not recommended in children because the benefits are minimal and there is potential for adverse effects on growth and development.

Hypertension is fairly common in older children with ADPKD and should be treated. In adults with ADPKD, rigorous control of blood pressure was superior to standard control in reversing left ventricular hypertrophy.[167] There is not a consensus on the ideal class of antihypertensive agent to select for these patients. Despite the pathogenic role of the renin–angiotensin system,[124] and the evidence that ACE inhibitors slow the progression of renal insufficiency in a variety of kidney diseases,[168,169] ACE inhibitors, when rigorously tested, do not slow the progression of chronic kidney disease in ADPKD.[169] ACE inhibitors do reverse left ventricular hypertrophy in hypertensive adults with ADPKD,[170] but there is a small risk of precipitating acute renal failure in patients with ADPKD, and thus they

must be used cautiously.[171] Other agents, such as calcium channel blockers, have also been advocated.[172]

The goal of therapy is normalization of blood pressure using standard guidelines.[173] In adults with ADPKD, low targets for blood pressure may have a deleterious effect on renal function.[166]

UTIs should be treated promptly, with awareness for the increased risk of abscesses and septicemia. Cyst infection requires selection of an antibiotic that penetrates the cyst, such as trimethoprim-sulfamethoxazole[174] or ciprofloxacin;[175] occasionally, cyst aspiration may be necessary.[176] Patients with intractable pain from renal cysts can benefit from cyst aspiration, surgical reduction, or thoracoscopic denervation.[177,178] Very rarely, nephrectomy may be indicated for recurrent UTIs, intractable chronic pain, and significant hematuria requiring ongoing transfusions or to accommodate the allograft.[179]

The possibility of a ruptured intracranial aneurysm is a frightening, albeit rare complication in pediatric patients. The advisability of screening patients is currently debated. Magnetic resonance angiography (MRA) is a safe and sensitive approach for detecting an asymptomatic aneurysm.[149] However, there is a need to balance the safety and efficacy of surgical intervention with the risk of aneurysm rupture. One decision analysis supported screening a 20-year-old patient with ADPKD,[180] although others have suggested a less aggressive approach.[181,182] Because of the familial predilection to aneurysm formation,[149,150] screening of older teenagers with a positive family history is a reasonable approach.[183] However, patient selection and timing and frequency of screening continue to evolve.[184,185]

Prognosis

Most children with ADPKD have minimal symptoms throughout childhood. The adult course of the disease is extremely variable.

There are currently limited data on the ultimate prognosis for patients diagnosed during childhood. This is especially true for patients with asymptomatic cysts; the impact of increased numbers of cysts on the risk of chronic kidney disease is unknown. Children who are diagnosed after the neonatal period do not have a decrease in GFR, even in the subgroup with more cysts and symptoms.[119] In adults, the presence of the *PKD1* gene, younger age at diagnosis, male gender, hypertension, increased left ventricular mass, hepatic cysts in women, three or more pregnancies, gross hematuria, UTI in men, proteinuria, and renal volume are all independently associated with poor renal function.[152,186] In children, increased renal volume in early life or hypertension is associated with subsequent faster renal growth, a potential marker of a worse prognosis.[187] There seems to be a higher risk of early chronic kidney disease when patients have more severe disease as children.[118]

Interestingly, many children diagnosed antenatally have normal renal function,[28] although follow-up is relatively limited. The cases diagnosed neonatally frequently have severe, often fatal, disease. These children are at risk for early chronic renal insufficiency and ESRD. However, others maintain normal renal function throughout childhood.[102]

NEPHRONOPHTHISIS

NPHP, also called juvenile NPHP, is one of the most common causes of chronic kidney disease in children.[188] NPHP, which is recessively inherited, is often grouped with dominantly inherited medullary cystic disease because of an overlapping radiologic and histologic appearance. However, medullary cystic disease is genetically distinct, lacks extrarenal involvement, and usually presents in adulthood. We will therefore consider it separately later in this chapter.

Genetics

Mutations in 13 genes (*NPHP1–NPHP11*, *AHI1*, and *CC2D2A*) have been identified that cause NPHP (Table 23.7), and additional genetic heterogeneity is likely.[189–196] These genes encode components of the ciliary apparatus, composed of the primary cilia, basal bodies, or centrosomes.[197,198] Mutations in the *NPHP1* gene are the most common cause of NPHP.[199,200] Most patients with NPHP

TABLE 23.7 Genetic heterogeneity of NPHP

Type	Chromosome locations	Gene mutated	Encoded protein
NPH type 1	2q13	*NPHP1*	Nephrocystin
NPH type 2	9q22	*NPHP2*	Inversin
NPH type 3	3q22	*NPHP3*	Nephrocystin 3
NPH type 4	1p36	*NPHP4*	Nephrocystin 4
NPH type 5	3q21	*NPHP5*	Nephrocystin 5/IQCB1
NPH type 6	12q21	*NPHP6*	Nephrocystin 6/CEP290
NPH type 7	16p	*NPHP7*	GLIS2
NPH type 8	16q	*NPHP8*	RPGRIP1L
NPH type 9	17q11	*NPHP9*	NEK8
NPH type 10	1q44	*SDCCAG8*	SDCCAG8/CCCAP
NPH type 11	8q22	*MKS3*	Meckelin
AHI1	6q23	*AHI1*	Jouberin/AHI1

type 1 are homozygous for a large deletion that affects the *NPHP1* gene.[199,201]

Pathology

Grossly, the kidneys are often small and have a pale, finely granular surface.[202,203] On light microscopy, there is diffuse interstitial fibrosis with a mononuclear cell infiltration.[202,204,205] Along with tubular atrophy, there is extreme thickening and lamination of the tubular basement membranes.[202,204] Electron microscopy confirms this thickening, and also shows splitting of the basement membrane.[202] Sudden variation from one histologic abnormality to another is highly suggestive of NPHP.[206] In a child with a biopsy early in the course of the disease, tubular basement membrane thickening was the only histologic abnormality.[205] Cysts appear to originate from the distal convoluted tubules and collecting ducts.[204] The glomeruli may be normal or have periglomerular fibrosis with thickening of Bowman's capsule; glomerular obsolescence eventually develops.[202]

Clinical Features

Polyuria and polydipsia are due to poor urinary concentrating ability, and this can lead to problems such as dehydration, nocturia, and primary or secondary nocturnal enuresis.[202,207,208] Renal sodium wasting[202] leads to salt craving in some children.[207] The urinalysis is notable for the absence of abnormalities,[202,203,207] although low levels of proteinuria, usually tubular in origin,[208] are sometimes present. Glucosuria is also occasionally present.[208,209] Probably due to the polyuria and salt wasting, hypertension is unusual,[203,210] except in patients with NPHP type 2. Symptoms of chronic kidney disease, such as fatigue, anorexia, and growth retardation, are frequently present.[203,207,208,211] Symptoms of renal osteodystrophy may be the initial complaint.[211] Children with NPHP have anemia that is out of proportion to their degree of renal failure, and thus often have very low hemoglobin levels and notable pallor.[203,207,208,211,212] The anemia appears to be due to decreased erythropoietin production.[213] Growth is decreased, initially due to chronic dehydration and later due to renal insufficiency. NPHP may be associated with liver fibrosis with development of hepatomegaly and portal fibrosis, which is different from the biliary dysgenesis seen in classic congenital hepatic fibrosis.[57] A mutation in the *NPHP3* gene was described in a patient with NPHP and liver fibrosis.[194]

The majority of patients with NPHP type 1 develop ESRD at a mean age of about 10–13 years.[202,214] The defect in urine concentrating ability can lead to severe dehydration and acute renal failure, which may accelerate the development of chronic kidney disease.[214]

NPHP type 2 is distinct from the other forms of NPHP. Renal failure occurs in infancy, and the kidneys are large with widespread cysts.[198,215] Hypertension is more common than in the other forms of NPHP. *NPHP2* gene defects may also lead to situs inversus in a minority of children.[198] The timing of ESRD is fairly similar in NPHP type 1 and NPHP type 4, while ESRD develops at about a mean age of 19 years in NPHP type 3.[214,216]

Based on the median age of onset of ESRD, the clinical variants are described as infantile (1 year of age), juvenile (13 years of age), and adolescent (19 years of age), with specific gene defects associated with each variant.[197] Infantile *NPHP* is associated with mutations in the *NPHP2* gene, leading to ESRD by 1–3 years. The juvenile form is the most common. Juvenile NPHP is most commonly due to *NPHP1* gene mutations. *NPHP3* gene mutations are common with the adolescent variant.[194]

Senior–Løken syndrome is the combination of NPHP with tapetoretinal degeneration,[217,218] and it is seen in 10%–15% of cases.[196] In the early-onset form, called congenital amaurosis of Leber, nystagmus is usually present, and there is an absent pupillary response to light. The retina is markedly abnormal on funduscopic examination; findings include arteriolar narrowing, pale optic discs, and granular pigmentation of the fundus.[219] Most patients are blind or severely visually impaired, and have a flat electroretinogram.[208] There is a late-onset form of Senior–Løken syndrome in which visual impairment develops during childhood. Moreover, patients with a defect in the *NPHP1* gene may have ocular findings, including areas of retinal atrophy with flat or low-voltage electroretinograms. However, these patients are usually asymptomatic, and probably should not be considered to have Senior–Løken syndrome.[210,220,221] Senior–Løken syndrome is most commonly seen in association with mutations of *NPHP5* and *NPHP6*, although it may occur with other genes.[222,223]

Some children with NPHP have other extrarenal manifestations, including mental retardation,[202,212,224] hepatic fibrosis,[202,224–227] Dandy–Walker syndrome,[212] cerebellar ataxia,[226,228] coloboma,[202] and skeletal anomalies.[202,226,228–230] However, there is some question about the rigor of the renal diagnosis in some of these cases.[231]

Mutations in the *NPHP1* gene have been associated with extrarenal manifestations, including Joubert syndrome,[232] ocular motor apraxia Cogan type,[233] and the combination of cerebellar ataxia and nystagmus.[234] Mutations in the *NPHP3* gene can cause hepatic fibrosis or tapetoretinal degeneration.[194] Mutations in the *NPHP4* gene can cause ocular motor apraxia Cogan type or tapetoretinal degeneration.[189,235] Mutations of *NPHP5*, *NPHP6*, and *NPHP10* genes are associated with retinitis pigmentosa.[236]

The more common possible extrarenal manifestations of NPHP are shown in Table 23.8. Many patients with extrarenal manifestations also have tapetoretinal degeneration, and thus are part of the Senior–Løken syndrome.

TABLE 23.8 Extrarenal manifestations in NPHP

Tapetoretinal degeneration
Liver fibrosis
Skeletal abnormalities
Mental retardation
Cerebellar ataxia
Situs inversus
Cardiac malformations

Other syndromes associated with NPHP include Jeune syndrome (asphyxiating thoracic dysplasia),[237] Ellis–van Creveld syndrome,[238] Alstrom syndrome (retinitis pigmentosa, deafness, obesity, and diabetes),[239] RHYNS syndrome (retinitis pigmentosa, hypopituitarism, NPHP, and skeletal dysplasia),[230] Bardet–Biedl syndrome (obesity, cognitive impairment, retinal dystrophy, microorchidism in males, polydactyly, and renal abnormalities),[240] Meckel–Gruber syndrome,[241] Mainzer–Saldino syndrome (NPHP with cone-shaped epiphyses of the phalanges),[228] and Arima syndrome (cerebro-oculo-hepato-renal syndrome).[242]

Radiologic Features

By ultrasound, the kidneys are hyperechoic with loss of corticomedullary differentiation; they are of normal or slightly decreased size.[243–245] Medullary cysts are a hallmark of the disease, but they are not always detected by ultrasound.[207,243,244] CT is a more sensitive method for identifying medullary cysts[246] and thin-section CT is recommended.[207]

Diagnosis

The diagnosis of NPHP can be challenging, especially in patients without extrarenal manifestations. A history of polyuria and polydipsia, salt craving, disproportionate anemia, a benign urinalysis, and the age of presentation are important clues. The detection of medullary cysts in the setting of chronic kidney disease in a child and smallish, echogenic kidneys is virtually diagnostic. The presence of consanguinity or an affected sibling suggests an autosomal recessive disease, and thus strongly supports the diagnosis. Renal histology is potentially helpful in uncertain cases. Genetic diagnosis is now possible and is commercially available, although the large number of genes, some not yet identified, limits sensitivity. All patients should have an ocular examination to screen for Senior–Løken syndrome and a liver ultrasound to screen for hepatic fibrosis.

Treatment

There is no specific therapy for NPHP. Families should be counseled regarding the risk of dehydration due to polyuria. The anemia responds to erythropoietin. Children receive standard therapy for chronic kidney disease and ultimately require dialysis and transplantation. The disease does not recur in the kidney transplant, and thus transplant is usually quite successful.[219,247] Appropriate specialist care is necessary in children with extrarenal manifestations.

MULTICYSTIC DYSPLASTIC KIDNEY

Multicystic dysplastic kidney (MCDK) is the most common cystic disease diagnosed during childhood. Most cases are unilateral and asymptomatic; rare bilateral disease is usually fatal at birth due to Potter syndrome.[248] The widespread use of prenatal ultrasound has led to more frequent diagnosis of MCDK, and the approach to the management of these patients is evolving.

The incidence of MCDK is estimated at 1 in 2500 newborns;[249] it is one of the most common fetal anomalies detected by prenatal ultrasound. It occurs slightly more commonly in the left kidney,[250] and the affected child is more likely to be male.[251,252] Given the low incidence of unilateral renal agenesis in neonates, and the much higher incidence of single kidneys in adults, the majority of adults with a single kidney had an MCDK that involuted over time.

MCDK is typically composed of cysts of varying size that do not appear to communicate, separated by a small amount of abnormal-appearing renal parenchyma. The ureter from the affected kidney is atretic. On microscopic examination, the tissue between the cysts is dysplastic, with undifferentiated mesenchymal cells, often with cartilage, and immature glomeruli and tubules. Occasionally, a few normal-appearing nephrons may be present, explaining the minimal renal function that is infrequently demonstrated on nuclear scan.

Most cases of MCDK are sporadic,[253] although families with putative autosomal dominant inheritance have been described.[253,254] The incidence of MCDK is increased in a variety of syndromes.[255] The pathogenesis of MCDK has been attributed to either early ureteral obstruction[256] or disruption of the normal mechanism of induction of the metanephric blastema by the ureteric bud.[257]

Currently, most MCDKs are diagnosed by prenatal ultrasound, with palpable abdominal mass, typically in the neonate, as the second most common presentation.[258–260] There are rare cases of diagnosis due to symptoms such as emesis or respiratory compromise from compressive effects.[261] In older children, MCDK is uncommonly diagnosed during the evaluation for abdominal pain or mass, hematuria, or hypertension. In all ages, MCDK may be discovered during the evaluation for UTI or as incidental finding during abdominal imaging.[262,263]

The diagnosis of MCDK is typically made by ultrasound. In infants with a prenatal diagnosis, a postnatal ultrasound should be performed to confirm the presence of MCDK. The major diagnostic dilemma is differentiation from hydronephrosis.[264] In MCDK, there is typically no communication between cysts, and the larger cysts are not medial. In hydronephrosis, the calyces extend outward from the dilated renal pelvis, and there is renal parenchyma surrounding the central cystic structure. The normal reniform shape is usually present with hydronephrosis, but usually absent in MCDK.[265] If the diagnosis is unclear, a radionuclide scan shows uptake of tracer if hydronephrosis is present, but usually no uptake with MCDK. Occasionally, MCDK demonstrates a small amount of uptake,[266,267] and other studies may then be useful in confirming the diagnosis.[264]

The contralateral kidney, if normal, undergoes compensatory hypertrophy, the absence of which suggests abnormalities of the contralateral kidneys.[268] Children with MCDK are more likely to have abnormalities of the contralateral kidney.[251,269,270] VUR has been reported in 4%–31% of contralateral kidneys,[250,251,269–271] with a majority of the patients showing a VUR of grade III or below.[272] Other reported anomalies include ureteropelvic

junction obstruction, ureteral ectopia, ureterovesical junction obstruction, ureteroceles, and renal dysplasia.[251,269,270]

The natural history of MCDK is usually gradual involution. The rate of involution is greatest in the first 2 or 3 years of life.[273] In one study, 18% were undetectable by ultrasound at 1 year of age, and 58% were undetectable by 6 years of age.[258] Some MCDKs do increase in size during the first few years of life, and complete involution may take more than 20 years.

Hypertension, which is postulated to be renin mediated,[274] has been reported as a potential complication of MCDK.[250,275] There are reports of hypertension being cured following surgical removal of the MCDK.[274] Yet, others have questioned the validity of these reports. For example, in a series of 260 cases, there were only 4 patients with hypertension, which was described as minimal and probably unrelated to the MCDK.[276] A more recent systemic review of 29 studies including 1115 patients found just 6 cases of hypertension, an incidence lower than that found in the general pediatric population.[277]

Malignancy is another possible complication of MCDK. There are cases of Wilms' tumor in younger children[278] and renal cell carcinoma in older teenagers and adults,[279] but some question the validity of these reports.[280] The true increase in risk is unclear. Less than 0.1% of the 7500 children enrolled in the National Wilms Tumor Study Group had an MCDK.[280] A recent systematic review concluded that the risk of malignancy is extremely low.[281]

The management of MCDK is controversial.[275,282,283] There has been a shift from routine surgical removal to nonoperative management, consisting of surveillance ultrasounds to monitor normal compensatory hypertrophy of the contralateral kidney and possibly to screen for Wilms' tumor.[276] There is not a consensus on the frequency of these ultrasound evaluations, especially given the low risk of Wilms' tumor. Ultrasounds are usually done more frequently during the first year of life (e.g., every 6 months), and then less frequently (e.g., every 12 months) until approximately age 5 years.[258] Surgical removal (discussed in Chapter 28) is indicated if there is any change that is suspicious for a Wilms' tumor. Other indications for nephrectomy include mass effect, pain, hypertension, and parental preference.

Follow-up, and surgical repair when indicated,[251] of the contralateral kidney is also critical. The follow-up ultrasounds of the MCDK should evaluate the size and echogenicity of the contralateral kidney; there should be compensatory hypertrophy.[250,270] Given the high rate of VUR, routine voiding cystourethrogram was frequently recommended,[284] although this has been questioned in the child with a normal-appearing contralateral kidney.[251,285] Routine monitoring of blood pressure, urinalysis to detect proteinuria, and follow-up of renal function, especially in the child with an abnormal contralateral kidney and potential risk for the development of chronic kidney disease, is recommended.[286]

MEDULLARY CYSTIC KIDNEY DISEASE

Medullary cystic kidney disease (MCKD) is frequently grouped with NPHP as the juvenile NPHP–medullary cystic disease complex.[287] However, MCKD is clearly a distinct entity, based on its autosomal dominant inheritance and later onset.[288] Renal failure typically develops during adulthood, although renal insufficiency may be apparent in some children.[235,288,289] In some families, the disease is not apparent until a mean age of more than 60 years.[290] Hyperuricemia and gouty arthritis, occasionally diagnosed in childhood,[289] may be the presenting manifestation.[291,292] Other clinical features include polyuria, anemia, and hypertension.[293,294] The kidneys are usually of normal size or small, and renal imaging may show a few medullary cysts, but the absence of visible cysts is relatively common.[289] The urinalysis is typically benign, except for low-grade proteinuria in a minority of patients.[293] Histologic examination demonstrates interstitial nephritis; thickening and splitting of the basement membrane is the most notable feature.[289,295]

MCKD is classified into four types, based on the underlying genetic mutations. Mutations in *UMOD*, the gene encoding uromodulin (also called the Tamm–Horsfall protein), cause MCKD type 2, and are present in the majority of cases.[296,297] Mutations in *UMOD* also cause the autosomal dominant disorder, familial juvenile hyperuricemic nephropathy (FJHN), and uromodulin-associated kidney disease (UAKD).[296,298] It is now clear that MCKD type 2 and FJHN are the same, since they are genetically allelic and clinically indistinguishable.[289,296,299] The dominant features are chronic kidney disease and gout.[295] Genetic diagnosis, by sequencing of exons 3 and 4, the site of most mutations in this disorder, is commercially available.

The locus for MCKD type 1 has been identified on chromosome 1.[290] These patients tend to have fewer manifestations of hyperuricemia than patients with MCKD type 2 and a later onset of renal insufficiency.[293] There is evidence for additional genetic heterogeneity.[293,300] Mutations in the REN gene, which encodes renin, have also been identified as a cause of MCKD.[301] Some families with MCKD have been identified without mutations in *UMOD*, *REN*, or the gene on chromosome 1, but with a new locus linked to chromosome 2.[302]

Treatment includes management of hyperuricemia with xanthine oxidase inhibitor (allopurinol). Patients also receive standard management of chronic kidney disease.

MEDULLARY SPONGE KIDNEY

Medullary sponge kidney (MSK) is predominantly a disease of adults, but it occasionally presents in childhood.[303–305] The intrapapillary collecting ducts are dilated, and multiple small cysts may be present. Not all renal pyramids are always affected, providing an explanation for the often asymmetric and focal appearance. This does not appear to be an inherited disease, although a few family clusters are described.[306,307]

The diagnosis of MSK is usually incidental, but it can be identified based on the characteristic changes on IVP, which shows stagnation of contrast in one or more renal papillae due to dilation of the collecting ducts (Figure 23.9). The resultant image has been described as a "pyramidal blush."[308] These changes are sometimes misdiagnosed as

FIGURE 23.9 IVP demonstrating bilateral MSKs in a 9-year-old girl who presented with hematuria. Note the characteristic radial stretching and puddling, which represent the contrast-filled dilated collecting tubules in this disease. (Adapted from Glassberg KI et al. Congenital anomalies of kidney, ureter and bladder. In Goldsmith HS, Karafin L, Kendall AR, eds., *Goldsmith's Practice of Surgery: Urology*. Hagerstown, MD: Harper & Row 1982, 1–82.)

papillary necrosis.[306] CT scan is not as sensitive for making the diagnosis of MSK, but it has a superior ability to detect the papillary calcifications that frequently complicate MSK.[304,309,310] Ultrasound also frequently detects this nephrocalcinosis, which may not be visible on a plain film.[304]

Clinically, patients are at increased risk for hematuria, UTI, and nephrolithiasis. There may be impairment of urinary concentrating ability[304] or urinary acidification (renal tubular acidosis [RTA]), but the GFR is normal.[311,312] The urinary concentrating defect can lead to complaints of polyuria in a child.[304] The increased risk of nephrolithiasis and nephrocalcinosis[313–315] is probably secondary to stagnation in the dilated collecting tubules and an increased incidence of hypercalcuria,[316] hypocitraturia, and hypomagnesuria.[317,318] Patients with RTA are more likely to have hypercalcuria or hypocitraturia, and the acidification defect may be the primary problem.[316,317,319] Nevertheless, even patients without a defect in urinary ion excretion have an increased risk of nephrolithiasis,[315] arguing for a role of the dilated tubules.[320]

The RTA in MSK, when present in a child, can lead to growth retardation.[305] RTA is sometimes associated with severe potassium wasting, and this can lead to symptomatic hypokalemia.[321]

Hematuria is usually mild, but massive bleeding is occasionally seen.[322] More commonly, MSK is the explanation for asymptomatic microscopic or gross hematuria, and these are frequent complaints in pediatric cases.[303,304]

The increased risk of UTI may be related to stasis in the dilated tubules and the presence of stones, which may cause obstruction or act as a nidus of infection. UTI in MSK is occasionally complicated by abscess formation.[323] A decrease in bone mineral density was also observed in young adults with MSK disease, and improvement was seen with potassium citrate therapy, according to one study.[324]

Associated anomalies reported with MSK include hemihypertrophy,[305,325–329] Caroli's disease,[330,331] hyperparathyroidism,[332,333] and a variety of miscellaneous disorders.[307,334,335]

Most patients require limited treatment. Nephrolithiasis is successfully treated by the usual approaches, including extracorporeal shock wave lithotripsy.[336] The plasma creatinine generally remains normal, but a stone-induced obstruction may cause a rise in creatinine. Patients with MSK and RTA have a good response to alkali therapy, with decreased hypercalcuria and stone formation.[316,337] UTIs are treated conventionally, with the caveat that an abscess should be suspected if the patient does not respond.[323]

GLOMERULOCYSTIC KIDNEY DISEASE

Glomerular cysts are present in a variety of diseases (Table 23.9); the diagnosis is made by kidney biopsy. The term *glomerulocystic kidney disease* (GCKD) is reserved for patients who do not have an underlying disease, such as ADPKD. Typically, these patients have cysts involving less than 5% of nephrons without associated tubular dilation. As detailed below, GCKD is not a uniform, well-defined entity; rather, it describes a heterogenous group of patients who have been grouped into categories based on apparent inheritance and kidney size.

Glomerular cysts may be seen in children with a variety of severe, usually inherited, malformation syndromes (Table 23.9).[338–345] Many of these patients have accompanying renal dysplasia. Again, these patients have glomerular cysts, but they do not have GCKD.

Glomerular cysts are seen in ADPKD, but most patients also have cysts involving other segments of the nephron.[146,346,347] However, there are cases of GCKD in children with a strong family history of ADPKD.[100,348] This suggests that in these patients, GCKD is a variant of ADPKD, with predominance of glomerular cysts. In fact, one child had GCKD on initial biopsy, but subsequently had pathologic findings consistent with ADPKD.[348] It has also been hypothesized that some patients with "sporadic" GCKD may, in fact, have ADPKD, either due to a new mutation or because of incomplete family studies.

TABLE 23.9 Diseases with glomerular cysts

Syndromes with glomerular cysts
Brachymesomelia–renal syndrome
Oral-facial-digital syndrome
Glutaric acidemia type II
Trisomy 18
Renal retinal dysplasia
Short-rib polydactyly syndrome type II
Tuberous sclerosis
Zellweger syndrome
Autosomal dominant polycystic kidney disease
Sporadic glomerulocystic kidney disease
Familial hypoplastic glomerulocystic kidney disease
Autosomal dominant glomerulocystic kidney disease

Children with sporadic GCKD have a variable presentation. The kidneys are frequently enlarged at birth, with a loss of corticomedullary differentiation.[349,350] Kidney size may normalize,[350] and occasionally the medulla is of normal echogenicity despite an echogenic cortex.[349] Ultrasound and MRI can identify cortical cysts.[49,351] Renal function may be normal[349,350] or decreased.[352,353] Other cases of sporadic GCKD present in adults; these patients may have mild[65,354] or severe[355–357] renal failure, typically with enlarged kidneys.

There is an autosomal dominant form of GCKD that is associated with small (hypoplastic) kidneys and malformed or absent calyces.[358,359] These children have a decreased GFR at birth, but then renal function remains fairly stable. Some of these patients have been growth retarded,[359] and a few have a noticeable prognathism.[358,359] In some families, hypoplastic GCKD is secondary to mutations in hepatocyte nuclear factor 1β (HNF-1β).[360–363] Heterozygous mutations in HNF-1β may also cause maturity-onset diabetes of the young (MODY), and thus affected patients may have renal disease and diabetes.[360–362] This combination is often referred to as renal cysts and diabetes (RCAD) syndrome. Other extrarenal symptoms, such as hypomagnesemia, hyperuricemia, increased liver enzymes, and genital anomalies, may be present with this syndrome.[364]

The remaining families with GCKD have normal or increased kidney size. In one family with apparent autosomal dominant inheritance, kidney size and kidney function are normal, but those affected have an abnormal ultrasound.[365] In another family, a 10-year-old girl with an affected father has a mildly depressed GFR.[366] Melnick et al.[367] describe three siblings and their father; all have normal kidney size but a decreased GFR. Finally, a large family with GCKD was extensively studied by Sharp and colleagues.[368] These patients have hypertension, and renal function ranges from normal to ESRD. The kidneys are large and echogenic; pelvocaliectasis and a hypoechoic cortical rim are additional sonographic features. Inheritance is autosomal dominant, and linkage analysis indicates that neither the *PKD1* gene nor the *PKD2* gene is responsible for this family's disease.[368]

SIMPLE RENAL CYSTS

The increased use of radiologic testing has led to the identification of more children with simple cysts, which may be solitary or multiple. The incidence of simple cysts increases with age.[369–372] Less than 0.3% of children have simple renal cysts, and they are usually not associated with subsequent problems.[373] Cysts in children usually do not increase in size, and single cysts are commonly located in the right upper pole.[373] However, the presence of even a single cyst in the context of an appropriate family history supports a diagnosis of ADPKD.[161] The incidence of simple renal cysts is increased in children with AIDS.[374] Simple renal cysts are rarely detected by fetal ultrasonography, and the majority resolve before delivery.[375]

Simple renal cysts do not impair renal function,[373,376] except in rare instances.[377] They may play a role in causing infection[378] or hypertension[370,377,379,380] in some patients. Cysts in children occasionally cause pain.[381,382] Symptomatic cysts can be treated by percutaneous drainage, although they usually recur unless a sclerosing agent is injected. Injection of the cyst with either alcohol[383,384] or tetracycline[381] prevents recurrence. Surgical marsupialization is rarely necessary. Because cysts frequently occur in the upper pole, it is sometimes difficult to differentiate a cyst from upper-pole hydronephrosis due to an obstructed ureterocele or an ectopic ureter. Such a diagnostic dilemma can be resolved by cyst aspiration.[381,385] Cyst fluid has the same blood urea nitrogen (BUN) and creatinine concentration as the patient.[385] In adults, the Bosniak renal cyst classification, based on CT findings, categorizes cysts into four categories, distinguishing benign cysts from cysts with the potential to be malignant.[386] This classification, although not validated in children, was used in a single-center study where 39 children were retrospectively identified (from 1996 to 2004) based on a modified Bosniak classification, to have complex renal cysts. Of the five children in whom surgical resection was performed, three revealed benign cysts, but the other two had renal cell carcinoma.[387] Most children with simple renal cysts only need routine ultrasound follow-up, unless the cysts are atypical and therefore suggestive of a malignancy.

MULTILOCULAR CYSTS

A multilocular cyst is a unilateral, benign tumor of the kidney. Approximately half the cases occur in children, with the remainder in middle-aged adults.[388] Children are more likely to be male, while adults are more likely to be female. Children are usually less than 2 years of age, and the most common presenting complaint is an abdominal mass.[388,389] Pathologically, the multilocular cyst is well encapsulated and noninfiltrating. The multiple cysts, which do not communicate, are typically separated by fibrous tissue, although embryonic tissue is sometimes present, especially in pediatric cases. The cysts are well visualized by CT scan or ultrasound. The differential diagnosis includes Wilms' tumor, ADPKD, or an MCDK. Occasionally, a second multilocular cyst appears months later in the contralateral kidney.[390]

Because of the possibility of a cystic Wilms' tumor, surgical resection is recommended.[388] Nephrectomy is sometimes the only option, but increasing numbers of cases are managed with renal-preserving surgery.[388,390]

ACQUIRED CYSTIC KIDNEY DISEASE

Kidney failure is sometimes associated with cyst formation in a previously noncystic kidney. Acquired cystic kidney disease (ACKD) occurs in patients with renal failure, including dialysis patients, transplant patients, and chronic kidney disease patients. ACKD occurs in children, and the number of cysts increases over time.[391–395] Acquired renal cysts are also common in children who have undergone liver transplantation.[396] In one case series, treatment with cyclosporine in these hepatic transplant patients was identified as the only independent risk factor.[397] Children with ACKD are at a low risk for gross hematuria and

retroperitoneal hemorrhage.[392] More ominously, a small percentage of children develop renal cell carcinoma.[393,395] Because of this possibility, periodic ultrasound screening of dialysis patients is necessary and children with suspicious lesions should have a nephrectomy.

SYNDROMES WITH CYSTIC KIDNEYS

A large number of syndromes are associated with cystic kidneys. These are mostly rare diseases, and many are neonatally fatal. We briefly review the major features of a few prominent entities, emphasizing those with a defined genetic etiology.

Tuberous Sclerosis

Although classified as one of the neurocutaneous syndromes, renal involvement is an important cause of morbidity and mortality in tuberous sclerosis (TS).[398,399] Patients with TS develop hamartomas in a variety of organs, including angiomyolipomas of the kidneys. The major extrarenal manifestations of TS are summarized in Table 23.10. Most of the features of TS become more prominent over time, except for cardiac rhabdomyomas, which tend to regress during childhood.[400] The hypopigmented macules (ash-leaf spots) are especially helpful diagnostically since they are often visible at birth and are eventually present in more than 97% of children;[401] use of a Wood's lamp, especially in light-skinned individuals, may aid in their identification. Facial angiofibromas, which may be confused with acne, and Shagreen patches are also extremely common. Neurologic lesions include multiple calcified tubers, disorders of neuron migration, and giant cell astrocytomas. The neurologic manifestations, with both seizures and developmental delay, are often the dominant clinical feature. Tumors of the kidney are the most common cause of malignancy in TS, but a variety of extrarenal cancers are also seen in adults and children.[402,403]

TABLE 23.10 Extrarenal manifestations in TS

Neurologic
Cortical tubers
Seizures
Mental retardation
Intracranial aneurysms
Retinal hamartoma
Cutaneous
Hypopigmented macules
Facial angiofibromas
Shagreen patch
Café-au-lait macules
Molluscum fibrosum pendulum
Forehead fibrous plaque
Periungual fibromas
Confetti-like macules
Cardiac
Rhabdomyomas
Wolf–Parkinson–White syndrome
Bone
Sclerosis
Cystic changes
Pulmonary lymphangiomyomatosis

TS is an autosomal dominant condition, but two-thirds of the cases are due to new mutations, so most patients will not have a positive family history. There is variable penetrance, and thus affected parents usually have mild disease and may be undiagnosed. TS is caused by mutations in either the *TSC1* gene on chromosome 9[404] or the *TSC2* gene on chromosome 16.[405] Both of these genes encode tumor suppressors, and the hamartomas arise because of mutations in the normal wild-type gene.[406,407] Intellectual disability is more common in patients with mutations in the *TSC2* gene.[408,409] The *TSC2* gene is located adjacent to the *PKD1* gene on chromosome 16.[79] Some children have large chromosomal deletions that affect both the *TSC2* gene and the *PKD1* gene, and these children tend to have severe polycystic kidney disease.[79,410] This contiguous gene syndrome is present in the majority of children with early, severe polycystic kidney disease and TS.[411]

Angiomyolipomas are the most common renal lesion in TS and are readily seen by CT or ultrasound (Figure 23.10). Angiomyolipomas are usually not detected in the first few years of life, but they are ultimately found in most children with TS and they tend to increase in size during childhood.[412,413] Larger angiomyolipomas are sometimes associated with pain.[399] Hematuria is uncommon.[414] However, retroperitoneal bleeding from angiomyolipomas can be life threatening[398] and presents with sudden flank pain, a palpable abdominal mass, and symptoms of anemia. Clinical manifestations of angiomyolipomas are relatively uncommon in children.[415,416] In a study of 149 patients with TS, with the majority showing angiomyolipoma on ultrasound, only 19 gave a history of flank pain or hematuria on detailed surveys. This study also showed that the larger lesions (>3 cm) had increased risk for bleeding, but most patients remained asymptomatic.[417]

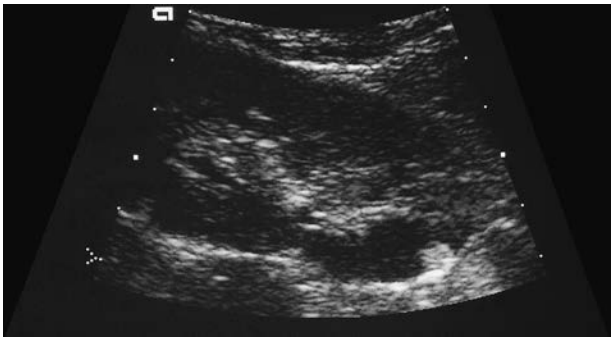

FIGURE 23.10 Ultrasound of a child with angiomyolipomas due to TS. This case nicely shows the hyperechoic fat (without shadowing) of an angiomyolipoma. (Courtesy of Dr. J. Sty, Children's Hospital of Wisconsin, Milwaukee.)

FIGURE 23.11 Renal CT of a child with cysts due to TS. Multiple cysts are visible. (Courtesy of Dr. J. Sty, Children's Hospital of Wisconsin, Milwaukee.)

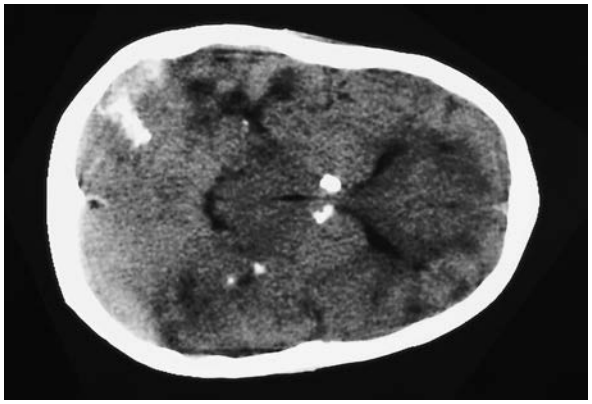

FIGURE 23.12 Head CT of the same child shown in Figure 23.11. Subendymal calcific densities are present in the region of the foramen magnum. (Courtesy of Dr. J. Sty, Children's Hospital of Wisconsin, Milwaukee.)

Renal cysts (Figure 23.11) are less common than angiomyolipomas and sometimes disappear on subsequent evaluation.[412] Renal malignancies, including renal cell carcinoma and malignant angiomyolipomas, are a serious concern in TS, and both are seen in children, sometimes in early childhood.[402,412]

Both renal cysts and angiomyolipomas cause destruction of normal renal tissue, and this can lead to renal failure in adults[418] and children.[411] The risk of renal failure and hypertension is greater in patients with cystic disease.[419–421] Children with disruption of the contiguous *PKD1* and *TSC2* genes usually have severe cystic disease and are at high risk for hypertension and early kidney failure.[411]

The diagnosis of TS is based on the classic clinical features, although genetic testing is commercially available. The possibility of TS should be suspected in a young child with large renal cysts suggestive of early-onset ADPKD. These children may have the contiguous gene syndrome with a deletion affecting both the *PKD1* and *TSC2* genes. A family history of TS is often not present due to variable penetrance and a high rate of new mutations. A search for skin manifestations is usually helpful, although cutaneous manifestations are less prominent or sometimes absent in infants.[401] Young children have fewer cortical tubers than older patients, but MRI is quite sensitive for detecting other subtle findings in infancy.[422] While MRI is more sensitive, most children have the mineralized subendymal nodules that are visible by CT (Figure 23.12).

Children with TS require the input of multiple specialists. All children with TS should have a renal ultrasound at diagnosis and follow-up renal ultrasounds every 1–3 years, with frequency dictated by the specific clinical situation.[423] Patients with extensive or rapidly changing lesions require more frequent follow-up. Those with more severe kidney disease may require CT or MRI to screen for malignant changes. Differentiating angiomyolipomas from malignancy requires careful comparison of sequential images. Patients with kidney failure are treated with dialysis[418] and transplantation.[424] Because of the risk for renal hemorrhage and malignancy, there is an argument for bilateral nephrectomies in children who progress to ESRD, especially those with large angiomyolipomas.

Meckel Syndrome

Meckel syndrome, sometimes called Meckel–Gruber syndrome, is a lethal autosomal recessive disorder. The most common extrarenal manifestations are posterior encephalocele, polydactyly, and hepatic fibrosis and cysts; however, a variety of other findings may also be present.[425,426] Cystic dysplasia of the kidneys is present in all cases.[425,426] Multiple genetic loci for Meckel syndrome have been identified.[241,427–429]

von Hippel–Lindau Disease

von Hippel–Lindau (VHL) disease is a rare autosomal dominant disorder with variable penetrance. The most prevalent manifestations are cerebellar hemangioblastoma, retinal angioma, pancreatic cysts, renal cell carcinoma, spinal hemangioblastoma, and pheochromocytoma.[430,431] Renal cysts are also common, but like renal cell carcinoma, they are rarely seen in childhood.[430,431] A mutation in a tumor suppressor gene, located on chromosome 3, causes VHL;[432] genetic testing is commercially available.

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CHAPTER 24

Acute Kidney Injury

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INTRODUCTION

Acute kidney injury (AKI), previously referred to as acute renal failure, is defined as a sudden decrease in kidney function that compromises the normal renal regulation of fluid, electrolyte, and acid–base homeostasis. In practical terms, AKI is characterized by a reduction in the glomerular filtration rate (GFR), which results in an abrupt increase in the concentrations of serum creatinine and blood urea nitrogen (BUN).[1] In 2002, the Acute Dialysis Quality Initiative Group introduced the RIFLE (acronym for risk for renal dysfunction, injury to the kidney, failure of kidney function, loss of kidney function, and end-stage renal disease) criteria in order to stage AKI. RIFLE aimed to standardize the definition of AKI by stratifying patients based on changes in the serum creatinine levels from baseline and/or an abrupt decrease in urine output.[2] The RIFLE criteria were found to be independent predictors of length of stay, costs, morbidity, and mortality in adults.[3] Subsequently, a modified pediatric RIFLE, or pRIFLE, was developed to stage AKI in children (Table 24.1).[4]

As highlighted by the RIFLE criteria, the urine volume in AKI is variable: patients may be anuric, oliguric, and in some cases, polyuric. AKI develops over a period of hours to days, whereas chronic kidney disease (CKD) develops over months to years. Short stature, renal osteodystrophy, delayed puberty, normocytic anemia, and hyperparathyroidism all suggest long-standing and advanced CKD rather than AKI. However, at a single point in time in an acute clinical presentation, it may be difficult to differentiate AKI from CKD without imaging studies, more extensive laboratory testing for the complications listed above, and possibly a kidney biopsy. Furthermore, at the time of presentation, a patient with CKD may have superimposed AKI, referred to as acute on chronic kidney disease.

AKI is usually encountered in pediatric urological patients as a complication of underlying chronic renal disease. The three most important contexts are acute pyelonephritis, aminoglycosides toxicity, and acute obstructive uropathy. Urologists must be alert to the possibility of AKI in any patient referred with bloody hematuria. The three most important contexts are urinary tract infection, glomerulonephritis, and myoglobinuria. Extracorporeal shock wave lithotripsy (ESWL) is the urologic treatment of choice for the majority of patients with renal or proximal ureteral stones.[5] Although rarely, bilateral or unilateral ESWL has been reported to be associated with AKI even in the absence of obstruction.[6] In order to most effectively diagnose the underlying cause of and treat the metabolic complications associated with AKI, all patients should undergo a full evaluation by a pediatric nephrologist at the time of presentation.

The likelihood of recovery from and appropriate treatment of AKI depends on the amount of urine output and the underlying cause. Quantifying the urine output is essential, as the amount of urine will often predict the clinical course and may aid in identifying the underlying renal insult. Patients with nonoliguric or high-output AKI (Table 24.2) have lower complication rates and higher survival than those with anuric or oliguric AKI.[7] Furthermore, children with acute interstitial nephritis or nephrotoxic renal insults, including aminoglycoside nephrotoxicity, are more likely to have AKI associated with either normal or increased urine output. In contrast, children with renal hypoperfusion injury, acute glomerulonephritis (AGN), hemolytic uremic syndrome (HUS), or other causes are more likely to have AKI associated with anuria or oliguria. The underlying cause of AKI may be classified as prerenal injury, intrinsic renal disease, or postrenal injury. It is important to note that some cases

TABLE 24.1 pRIFLE criteria

	Estimated GFR (eGFR)	Urine output
Risk	eGFR decreased by 25%	<0.5 mL/kg/h for 8 hours
Injury	eGFR decreased by 50%	<0.5 mL/kg/h for 16 hours
Failure	eGFR decreased by 75% or eGFR of <35 mL/min/1.73 m^2	<0.3 mL/kg/h for 24 hours or anuric for 12 hours
Loss	Persistent failure of >4 weeks	
End stage	End-stage renal disease (>3 months)	

Source: Adapted from Akcan-Arikan A et al. *Kidney Int* 2005;71(10):1028–35.

TABLE 24.2 Causes of nonoliguric AKI

Furosemide converting oliguric renal injury to nonoliguric renal injury
Nephrotoxins
Nonfulminant acute viral hepatitis
Primary lymphoma of the kidney
Severe exertional rhabdomyolysis
Hemolytic uremic syndrome

of AKI may be multifactorial, especially in hospitalized children.

PRERENAL INJURY

In prerenal AKI, renal function may be initially normal, but severe and/or prolonged renal hypoperfusion leads to renal injury and AKI. Prerenal AKI results from renal hypoperfusion caused by intravascular volume contraction, decreased effective circulating blood volume, or altered intrarenal hemodynamics. True intravascular volume contraction results from dehydration, acute blood loss, or extravascular accumulation of fluid—the so-called third spacing of fluid. This is most often encountered in patients with the systemic inflammatory response syndrome or with hypoalbuminemia. Infants are particularly vulnerable to excessive volume loss. They have a proportionally higher percentage of insensible water losses and, in addition, cannot maximally concentrate their urine as a result of immature kidneys. Decreased effective blood circulation occurs when the true blood volume is normal or increased, but renal perfusion is decreased. This commonly occurs in left-sided heart failure, cardiac tamponade, or hepatorenal syndrome.[8] Intrarenal afferent arteriolar vasoconstriction occurs in hepatorenal syndrome, calcineurin toxicity, and nonsteroidal anti-inflammatory drug (NSAID) use; intrarenal efferent arteriolar vasodilation occurs with the use of angiotensin-converting enzyme inhibitors (ACEIs). Afferent arteriolar vasoconstriction or efferent arteriolar vasodilation decreases the glomerular filtration.

In prerenal AKI, the kidneys are intrinsically normal and the reduced GFR and urine output are appropriate physiologic responses to the reduced renal blood flow. In the early stages, restoration of renal perfusion results in a prompt return of renal function to normal. If the insult is prolonged, acute tubular necrosis (ATN) may develop and the AKI will not immediately correct with improved renal perfusion. This signifies the progression to intrinsic renal disease. The evolution from prerenal injury to intrinsic renal disease is a gradual process because there are a number of compensatory mechanisms that maintain adequate renal perfusion. The two primary mediators of the intrarenal compensatory mechanism are the prostaglandins (PGI_2, PGE_2, and PGD_2) and angiotensin II. The prostaglandins promote compensatory vasodilation of the glomerular afferent arterioles in an attempt to maintain adequate blood flow and preclude further deterioration of renal function.[9] Angiotensin II causes a preferential constriction of the glomerular efferent arterioles, which increases glomerular filtration pressure.[10] The dilation of the afferent arteriole and constriction of the efferent arteriole work in concert to promote an increased filtration fraction and thereby maintain the GFR. Furthermore, angiotensin II, through direct action on the proximal tubule and through the effect of aldosterone on the distal tubule, causes increased sodium and water reabsorption. This helps to maintain an appropriate intravascular volume at the expense of a decreased urine output.

INTRINSIC RENAL DISEASE

When AKI is the result of intrinsic renal pathology, attempts are made to define the location of the insult. Renal injury may occur at the level of the renal vasculature, tubules, interstitium, or glomeruli. The basic mechanisms of renal injury include hypoperfusion, ischemic cell damage, toxin-mediated cell injury, and inflammation. The inevitable outcome is varying degrees of cellular death as a result of necrosis or apoptosis.[11]

Vascular Injury

Vascular injury may occur in large vessels, such as in renal artery thrombosis and renal venous thrombosis (RVT), or in the microvasculature, as in HUS and thrombotic thrombocytopenic purpura (TTP). Both renal artery thrombosis and RVT occur most commonly in newborn infants, while HUS is most common in young children. Conversely, TTP is rarely seen in pediatrics. Renal artery thrombosis is often associated with umbilical artery catheters and may result in hypertension. AKI rarely occurs unless there is a solitary kidney or the thrombosis is bilateral. In newborns, RVT is associated with maternal diabetes, polycythemia, and sepsis. Coagulation defects are increasingly being identified in neonates with RVT. In childhood, RVT is more closely associated with severe dehydration, nephrotic syndrome, and congenital hypercoagulable states.[12] RVT may present with large palpable kidneys, gross hematuria, hypertension, or oliguria. The neonate with RVT is usually very ill, but the condition may also be clinically silent.

The classic triad seen in HUS is acute hemolytic anemia with fragmented erythrocytes, thrombocytopenia, and AKI. The illness is usually preceded by an episode of acute gastroenteritis, often accompanied by bloody diarrhea. Sudden onset of pallor usually develops several days after the diarrheal illness resolves. Oliguria is a common feature, and one clue to making an early diagnosis is that the urine output remains decreased even with appropriate rehydration. The condition is usually caused by *Escherichia coli* O157:H7, a Shiga toxin–producing strain. The Shiga toxin is directly toxic to the glomerular vascular endothelium, where it initiates local coagulation (thrombotic microangiopathy), and to renal tubules, where it induces ATN. Several other strains of *E. coli*, as well as *Shigella dysenteriae* and *Aeromonas*, produce similar toxins that cause HUS. Non-diarrhea-associated HUS is a much less common condition caused by *Streptococcus pneumoniae* infections. Additional causes include bone marrow transplantation, HIV

infection, and medications. Inherited causes include deficiencies of factor H, factor I, and membrane cofactor protein (CD46).

Glomerular Injury

AGN is common in school-aged children but rare in children under the age of 2 years. Postinfectious glomerulonephritis is the most common cause in childhood. Antiglomerular basement membrane (GBM) antibody disease, anti-neutrophil cytoplasmic antibody (ANCA)-positive (pauci-immune) glomerulonephritis, lupus nephritis, immunoglobulin A (IgA) nephropathy, Henoch–Sconlein purpura nephritis, and membranoproliferative glomerulonephritis all cause AKI.[11] The clinical features of AGN include hypertension, oliguria, painless cola-colored gross hematuria, and edema that is more often periorbital than pedal; laboratory findings include proteinuria, red blood cell (RBC) casts, an increased serum creatinine concentration, evidence of antecedent streptococcal infection, and a low-serum-complement C3 concentration. Glomerular hypercellularity and inflammation result in a decreased GFR, reduced urine output, retention of potassium, and signs of fluid overload. The tubules and interstitium are mostly spared during the inflammatory process. Each of the glomerulonephritides can progress rapidly (rapidly progressive glomerulonephritis [RPGN]); this is characterized by oligoanuria, rapidly rising serum creatinine, and extensive crescent formation on renal biopsy. A diagnosis of RPGN must be made as soon as possible because treatment with corticosteroids, often together with plasmapheresis, is essential in order to preserve renal function.

Tubular Injury

Tubular injury is also known as ATN and is the end result of either ischemic or toxin-mediated damage to the tubules. The tubular epithelial cells are particularly sensitive to anoxia and are vulnerable to toxins. The cells of the straight segment of the proximal tubule and the thick ascending limb of the loop of Henle are highly dependent on oxidative phosphorylation. This serves to maintain their high energy demand, which is required for their transport functions. As a result, they are particularly susceptible to ischemia and to nephrotoxins that disrupt energy supply or mitochondrial function.[13]

Ischemia-induced ATN is the result of renal hypoperfusion. If the insult is prolonged and severe, prerenal AKI may progress to ATN that is no longer immediately reversible with restoration of appropriate renal perfusion. Tubular epithelium damage results in the release of vasoactive compounds that increase afferent arteriolar resistance, thereby decreasing renal blood flow and perpetuating tubular injury. This process is known as tubuloglomerular feedback and plays an important role in the progression from renal hypoperfusion to tubular injury. The vasoconstriction is exacerbated by adrenergic stimulation, decreased intrarenal prostaglandin synthesis, and increased angiotensin II formation.[11] The decrease in GFR is further reduced by the intraluminal tubular obstruction caused by the debris formed from sloughing tubular cells as they undergo apoptosis. The denuded tubular epithelium allows tubular back-leak of glomerular filtrate into the medullary interstitium, where it is returned to the systemic circulation. Tubuloglomerular feedback, intraluminal tubular obstruction, and tubular back-leak are all interrelated in the complex pathogenesis of AKI.[14] Several other vasoactive compounds, including endothelin and nitric oxide, are implicated in the progression of AKI, but their roles are not fully elucidated.

The clinical course of ischemia-induced ATN is divided into the anticipation phase, initiating phase, maintenance phase, and recovery phase.[15] During the initiating phase, the only signs might be a slight decrease in urine output and a rise in serum creatinine concentration and BUN. The maintenance phase is characterized by oliguria, fluid overload, acidosis, hyperkalemia, and a more rapid decline in GFR, usually with oliguria or anuria. Polyuria in the context of increasing serum creatinine concentrations is known as nonoliguric AKI. The recovery phase is characterized by polyuria, kaliuresis, and hypokalemia, while the serum creatinine and BUN begin to return to normal. The recovery process may take weeks to months, and more subtle impairments of tubular function may persist for even longer. If the ATN is prolonged and severe, the child may develop cortical necrosis, which is often associated with only partial recovery of renal function.

Toxin-mediated ATN can be caused by many medications (Table 24.3), poisons, or endogenous toxins. Common nephrotoxic medications are aminoglycosides, amphotericin, acyclovir, cisplatin, and radiocontrast agents.[11]

Aminoglycoside nephrotoxicity occurs in 10%–26% of patients,[16] usually after 1 week of treatment, although the AKI may be delayed until after discontinuation of the medication. The renal injury usually presents with a decrease in urine concentrating capacity, and is usually transient, mild, and nonoliguric. Serum and urine electrolyte abnormalities range from combinations of hypokalemia, hypomagnesemia, and hypocalcemia to complete acquired Fanconi syndrome or an acquired Bartter syndrome.[16,17] Accumulation of aminoglycosides in the lysosomes of the proximal tubules induces cell necrosis and the excretion of low-molecular-weight proteins (beta$_2$-microglobulin) and brush border enzymes. Risk factors for aminoglycoside-induced AKI are old age, hypovolemia, preexisting renal insufficiency, multiple nephrotoxic agents, hypokalemia, hypomagenesemia, prolonged use, total lifetime exposure, and elevated peak and trough levels.[11,14] It is important to note that studies in humans are dogged by confounding variables of the critically ill, and that the choice of an aminoglycoside should not be governed by nephrological

TABLE 24.3 Nephrotoxins

Aminoglycosides	Amphotericin
Trimethoprim	Sulfinpyrazone
Acyclovir	Fluoroquinolones
Mefenamic acid	Cisplatin
NSAIDs	Acetaminophen
Iphosphamide	Calcineurins
Diethylene glycol	Paraquat

criteria; the dosing, however, must be adjusted for the level of GFR. In most cases, there is full recovery with no evidence of permanent kidney disease or CKD.

Patients with amphotericin B–induced renal injury often present with nonoliguric AKI. Amphotericin B injures many different nephron segments, as well as the collecting duct. In addition to toxin-mediated AKI, amphotericin B may also cause hypokalemia and hypomagnesemia. Distal renal tubular acidosis occurs as a result of back-leakage of hydrogen ions into the interstitium.[11] Risk factors for the development of AKI include maximal daily dose, duration of therapy, and concomitant use of calcineurin inhibitors. Acyclovir-induced AKI is usually nonoliguric and may present with microscopic hematuria. Acyclovir is relatively insoluble in urine and, by forming crystals within the renal tubule, causes intratubular obstruction and a reduced GFR. Risk factors for the development of AKI include high doses, rapid intravenous administration, hypovolemia, and preexisting renal disease.[11]

Radiocontrast-induced nephropathy is uncommon in children and is usually mild and transient. The pathogenesis is unclear. Risk factors for contrast nephropathy include underlying renal disease, dehydration, large doses of contrast media, congestive heart failure, diabetes mellitus, and use of NSAIDs and ACEIs.[14]

Poison-mediated ATN may occur from direct tubular toxicity, as in mercury poisoning, or from crystal formation, as in ethylene glycol and methanol poisoning. Both ethylene glycol and methanol are nontoxic until they are metabolized by alcohol dehydrogenase into their metabolites. Once their metabolites have been generated, crystals will form in the tubules, causing obstruction and AKI.[11]

Endogenous toxins that can cause ATN are myoglobin, hemoglobin, and uric acid. Pigment-induced ATN can be precipitated by either hemoglobinuria or myoglobinuria. Tubular injury results from the precipitation of pigment in the tubules and heme protein–induced oxidative stress.[14] Myoglobin- or hemoglobin-induced AKI is more likely to develop in the presence of dehydration, metabolic acidosis, severe muscle damage, or multiple organ failure. Rhabdomyolysis is caused by viral infections (influenza), medications (statins), seizures, prolonged exercise, or illicit drug use (Table 24.4). The diagnosis can be confirmed by an elevated serum creatine phosphokinase level. The association between cocaine and rhabdomyolysis has been widely reported, while the association with amphetamines has only been described in case reports. Cocaine appears to have direct toxic effects on skeletal muscle, as well as vasoconstrictive properties, which lead to muscle ischemia.[18] Several proposed mechanisms have been put forth to explain methamphetamine-induced rhabdomyolysis, although direct myocyte toxicity has never been demonstrated. Amphetamine users are often agitated and experience uncontrolled choreiform movements. The rhabdomyolysis might occur in a fashion similar to that of exertional rhabdomyolysis after exhaustive physical exercise.[18,19] Hemolysis occurs in sickle cell disease, immune-mediated hemolysis, or glucose 6-phosphate dehydrogenase (G6PD) deficiency.[14]

TABLE 24.4 Causes of rhabdomyolysis

Chronic and inflammatory myopathy	Muscular dystrophy
Metabolic myopathy	Trauma
Nonketotic hyperosmolar coma	Exercise
Viral myositis	Dystonia
Malignant hyperthermia	Cocaine/methamphetamine ingestion

Treatment of pigment-induced AKI includes volume expansion, forced diuresis with a loop diuretic, and alkalinization of the urine to increase pigment solubility.[11] An increasing serum creatinine concentration in the context of fluid overload is an indication for hemodialysis.

Tumor lysis syndrome can be caused by excessive release of uric acid, phosphorus, and cell products, usually during treatment of acute lymphocytic leukemia or B-cell lymphoma. The probable mechanism of injury is related to precipitation of uric acid crystals in the tubules with obstruction of urine flow. The highest risk for tumor lysis syndrome is with the most rapidly growing tumors or during induction chemotherapy.

Aggressive hydration with the administration of allopurinol helps to decrease the uric acid burden and the risk of tubular precipitation. Rasburicase (urate oxidase) is an effective alternative to allopurinol for rapidly reducing uric acid levels, improving patients' electrolyte status, and reversing AKI. Screening for G6PD deficiency is essential prior to rasburicase administration, as it may cause hemolytic anemia and methemoglobinemia in susceptible patients.[20] Dialysis may be necessary if the metabolic abnormalities cannot be controlled with the aforementioned medical management.

Interstitial

Interstitial nephritis most often occurs as a result of exposure to medications. It can also be the result of infections, systemic diseases, tumor infiltrates, or genetic conditions. In many cases, no cause is found. Medications commonly associated with interstitial nephritis include extended-spectrum penicillins, NSAIDs, sulfonamides, and rifampin. Almost every known medication has been implicated. The pathogenesis of medication-induced acute interstitial nephritis is thought to be a hypersensitivity type or allergic reaction that causes an inflammatory reaction, mainly in the medullary interstitium. Many patients are asymptomatic or have vague complaints. Typical symptoms include fever, rash, arthralgias, and flank pain. Urine output is usually increased or normal because this is the most frequent cause of nonoliguric AKI. It is important to note that interstitial nephritis does not present with gross hematuria or isolated microscopic hematuria, and the urine may be bland, or there may be combinations of microscopic hematuria, mild proteinuria, pyuria, white blood cell (WBC) casts, eosinophilluria, and peripheral eosinophillia. Acute pyelonephritis, Epstein–Barr virus (EBV), and cytomegalovirus (CMV) also cause interstitial nephritis. Sarcoidosis and tubulointerstitial nephritis uveitis (TINU) are rare causes.

Postrenal Injury

Congenital obstructive uropathies are among the most frequent causes of CKD in pediatrics; this is often erroneously referred to as AKI when the presentation is in the newborn child. AKI rarely is the result of postrenal obstruction outside, except when this occurs in solitary kidneys from either aplasia or transplantation. In pediatric individuals with two functioning kidneys, postrenal AKI will occur only with urethral obstruction, bladder neck obstruction, or bilateral ureteric obstruction because a single normal kidney has sufficient ability to maintain a normal GFR. Most patients with acute obstruction leading to AKI have oliguric AKI, although nonoliguric AKI can occur with partial obstruction. Renal calculi, ureteral blood clots, retroperitoneal fibrosis, neurogenic bladder, bladder tumors, and urethral strictures can cause an obstruction at different levels of the urinary tract and lead to AKI.[14] During acute obstruction, a decreased GFR is the result of a rise in the intraluminal tubular pressure. A further decline in renal function is caused by arteriolar vasoconstriction. A prompt diagnosis is necessary to provide appropriate urological intervention. Hydronephrosis detected by renal ultrasound is an important finding. All patients with suspected obstruction should undergo bladder catheterization, as it may be therapeutic as well as diagnostic. Percutaneous nephrostomy, lithotripsy, ureteral stenting, and urethral stenting are indicated when appropriate.

DIAGNOSTIC APPROACH TO AKI

History and Physical Exam

The history and physical exam can provide invaluable clues that help determine whether the AKI is a result of a prerenal, renal, or postrenal event. A careful review of the patient's past medical history, family history, medication use, trauma, and recent febrile illnesses is essential. Furthermore, a careful assessment of fluid intake and urine output can help to narrow the differential diagnosis, as well as dictate future management. A major purpose of the physical examination in a patient with AKI is to attempt to determine the effective circulating volume. The patient's weight, blood pressure (sitting and standing), and pulse rate provide important clues. On general examination, the patient must be carefully assessed for edema, state of hydration, pallor, petechiae, rashes, and abdominal signs of tenderness, bladder fullness, and visceromegaly. Careful cardiac and pulmonary examination are performed to determine the degree of fluid overload. Clues for systemic diseases, such as rash, jaundice, arthritis, or uveitis, must always be looked for.

Urine Studies

The urinalysis, urinary sediment, and urine indices are the most important factors in determining the cause of AKI. But these must never be interpreted on their own; each value must be interpreted in relation to clinical findings and serum chemistry results. A high urine specific gravity (SG) (in the absence of proteinuria) is suggestive of decreased effective circulatory volume and prerenal AKI. An inappropriately dilute SG suggests tubular injury or interstitial nephritis. A dipstick test that is >3+ indicates intrinsic AKI with glomerular damage. Less proteinuria (<2+) may be seen in prerenal AKI, ATN, and postrenal AKI. Protein excretion of greater than 2 g/24 h suggests glomerular injury. A positive urine dipstick for blood usually indicates hematuria. However, if there are no RBCs on microscopic examination, myoglobinuria or hemoglobinuria must be considered. RBCs with RBC casts strongly suggest a glomerular lesion, especially in conjunction with significant proteinuria. WBCs and WBC casts are seen in pyelonephritis, acute postinfectious glomerulonephritis, and acute interstitial nephritis. The urinary sediment in ischemic ATN is characterized by pigmented casts, granular casts, tubule epithelial cells and casts, and cellular debris.

Urine diagnostic indices that are particularly helpful in characterizing AKI include urine sodium and creatinine concentrations. When used in conjunction with the serum sodium and creatinine, the fractional excretion of sodium (FE_{Na+}) can be calculated:

$$FE_{Na^+} = \frac{Urine_{Na} \times Plasma_{Cr} \times 100}{Plasma_{Na} \times Urine_{Cr}}$$

The results of the FE_{Na+}, urine sodium, and urine osmolality can be used to differentiate between prerenal and intrinsic AKI. A low urinary sodium (<10 mmol/L) and a low FE_{Na+} (<1%) indicate avid sodium and water retention. This is characteristic of prerenal AKI in which the intact proximal and distal tubules are able to respond appropriately to renal hypoperfusion. Conversely, the damaged tubules in ATN are unable to efficiently reabsorb sodium, and this results in a high urine sodium concentration (>10 mmol/L) and a FE_{Na+} of >2%. Two important caveats when using the FE_{Na+} to assess AKI are underlying renal disease and the concurrent use of diuretics. In postrenal obstruction, the indices are more variable and not very helpful. Early in the course, they may resemble those of prerenal AKI, but as tubular damage progresses, the indices become more similar to those of intrinsic AKI.[11,14]

Blood Studies

Evaluation of the BUN and serum creatinine concentration are essential in making a diagnosis of AKI, but the serum electrolyte concentrations more important for morbidity and mortality. The serum potassium concentration must be monitored closely in a patient with oliguria, and even more so anuria. Life-threatening hyperkalemia, particularly in association with a metabolic acidosis, must be treated immediately. Hemoglobin, hematocrit, platelet count, and serum concentrations of calcium, phosphorous, bicarbonate, and albumin must be routinely evaluated in patients with AKI. Serologic tests for *streptococcal* infection and complement studies are indicated if there are signs of AGN. It has been traditionally taught that a BUN serum–creatinine serum ratio of >20 suggests prerenal AKI, while the ratio is about 10 in ATN. Unfortunately,

this ratio is affected by many factors, including a catabolic state and gastrointestinal bleeding, that negate its value in critically ill patients.[14]

Diagnostic Imaging

The two most helpful initial imaging studies in patients with AKI are a chest radiograph and a renal ultrasonography. Chest radiographs can help define whether there is significant cardiomegaly or pulmonary edema as a result of fluid overload. Renal ultrasonography is extremely useful when either obstruction or RVT is suspected. Additionally, if it is unclear whether the patient has AKI or CKD, the ultrasound may be diagnostic. In patients with AKI, the kidneys are often large and swollen. Conversely, the kidneys in CKD are often small, scarred, or dysplastic. In both instances, they lose the normal corticomedullary differentiation and are echogenic.

Renal Biopsy

A percutaneous renal biopsy may be indicated in children with AKI if the cause is unknown or if there is any suspicion of a crescentic glomerulonephritis.

Complications of AKI

The major complications of AKI (Table 24.5) are related to either metabolic dysfunction or fluid overload. The metabolic complications of AKI are hyperkalemia, metabolic acidosis, hypocalcemia, hyperphosphatemia, hyponatremia, and rarely uremia. Hyperkalemia is the single most life-threatening complication of AKI. Hyperkalemia is the result of impaired tubular secretion, a decreased filtration fraction, and extracellular shifts of potassium induced by acidosis. Peaked T waves are usually the first manifestation of cardiotoxicity, followed by prolongation of the PR interval and widening of the QRS complex. Prompt treatment of hyperkalemia is required in order to prevent ventricular tachycardia or fibrillation. Uremia is characterized by mental status changes, evidence of serositis, and bleeding diathesis as a result of platelet dysfunction. It occurs when urea and other waste products build up in the tissues because the kidneys are unable to eliminate them adequately.

There are multiple causes for hypocalcemia in AKI, which include hyperphosphatemia, decreased gastrointestinal calcium absorption, vitamin D deficiency, and parathyroid hormone (PTH) resistance. The most important acute reason is hyperphosphatemia. The hypocalcemia is usually mild and may cause tetany if markedly reduced. The hyperphosphatemia in AKI is the result of decreased renal excretion. Metabolic acidosis is very common in AKI. Declining renal function prevents the kidneys from excreting the net acids generated by diet and normal metabolic function. Paradoxically, metabolic acidosis increases the fraction of serum calcium in the ionized form, lessening the risk of hypocalcemia. Special attention must be paid to the serum ionized calcium concentration when correcting metabolic acidosis because tetany may ensue.

Patients with oliguric or anuric AKI commonly present with hypervolemia and fluid overload. The hypertension is usually caused by fluid overload, but it may also be the result of changes in vascular tone or activation of the renin–angiotensin system. If the fluid overload worsens, the patient may develop pulmonary edema and/or congestive heart failure.

TABLE 24.5 Complications of AKI

Fluid overload
Hypertension
Hyperkalemia
Hyponatremia
Metabolic acidosis
Hyperphosphatemia
Hypocalcemia
Hyperuricemia

Management of AKI

There are five main principles in managing AKI:

1. Maintaining appropriate renal perfusion
2. Avoiding nephrotoxic agents
3. Establishing fluid balance
4. Maintaining electrolyte and acid–base balance
5. Providing nutritional support

In many circumstances, with the important exception of glomerular nephritides, renal hypoperfusion is a predisposing factor to the development of AKI. Optimizing intravascular volume is a fundamental principle in preventing the development and progression of AKI. If children at risk for the development of AKI are adequately hydrated prior to a known incipient insult, the extent of the renal injury can often be decreased or even prevented. This is particularly important prior to the administration of contrast media, aminoglycosides, cisplatin, or amphotericin and in preoperative patients. Adequate hydration may also prevent severe AKI in HUS in some patients. Additionally, it is important to stop or avoid medications that cause intrarenal afferent arteriole vasoconstriction (NSAIDs) or efferent arteriole vasodilation (ACEIs). Even in well-hydrated patients, potential nephrotoxic agents should only be used when necessary and with special attention to dosing schedules and by monitoring serum concentrations.

Establishing fluid balance is perhaps the most challenging and critical step in managing AKI. Prerenal AKI is the most common situation in which intrinsic renal damage can be prevented. Any hypovolemic patient who presents with oligoanuric AKI has a potential prerenal component. The first step in managing a patient with potential prerenal AKI is fluid resuscitation with one or more rapid infusions of normal saline, without any potassium, unless the patent is hypokalemic as a result of diarrhea or a tubulointerstistial disease. Maintenance fluids and replacement of ongoing losses should not be neglected during this period of initial rehydration. If the urine output does increase after the patient is assessed to be euvolemic, intrinsic renal damage must be assumed. At this stage, in the absence of increased urine output, fluid restriction becomes essential

to avoid hypertension, pulmonary edema, and congestive heart failure. During fluid restriction, the patient should receive insensible losses (400–700 mL/m^2/24 h of D5W) plus urine output losses (milliliter per milliliter replacement with 0.45% NS). If the patient becomes hypervolemic after fluid resuscitation or requires large quantities of blood products or intravenous alimentation, a diuretic, such as furosemide, is administered in an attempt to increase urine output. Diuretics must be used with caution in the absence of good evidence of euvolemia or hypervolemia because they may worsen the component of AKI. Patients who present with nonoliguric AKI (acute interstitial nephritis or the recovery phase of ATN) may actually be polyuric and require greater than normal volumes of fluid to avoid intravascular volume depletion.[15]

Maintaining the electrolyte and acid–base balance involves managing hyperkalemia, hypocalcemia, hyperphosphatemia, and metabolic acidosis. All potassium must be removed from the intravenous fluids and in any patient with oligoanuric AKI. Treatment of hyperkalemia is indicated if electrocardiogram (EKG) abnormalities are noted or if serum concentrations are higher than 6–7 mEq/L. Treatment regimens are those that protect against hyperkalemia, those that redistribute potassium intracellularly, and those that remove it from the body.[11] Calcium gluconate is cardioprotective against the conduction abnormalities induced by hyperkalemia, but it does not remove potassium. Calcium gluconate is administered (0.5–1.0 mg/kg/dose) early in the course of treatment. Redistributive measures are albuterol, bicarbonate, and insulin plus glucose infusions. All three interventions begin to shift potassium intracellularly within 30 minutes; these are only temporizing measures, and the serum potassium concentration may rise rapidly after they are discontinued. Potassium can be removed from the body via the gastrointestinal tract or the kidney, or by dialysis. Sodium polystyrene (Kayexalate) administered at 1 g/kg exchanges sodium for potassium in the gastrointestinal tract and effects potassium removal. Hypernatremia is a common side effect from excessive sodium absorption. If the patient is not anuric, loop diuretics are used to promote potassium losses by kaliuresis. Dialysis is the definitive therapy in patients who do not respond to these regimens.[11]

Hypocalcemia is usually mild and responds to correction of the hyperphosphatemia and dietary calcium supplementation with calcium. Intravenous calcium infusion is indicated if there is tetany or arrhythmia. Hyperphosphatemia is treated by dietary restriction and oral phosphate binders. Calcium carbonate and calcium acetate are well-tolerated phosphate binders when taken with meals. The treatment of the metabolic acidosis is important for maintaining a normal pH for optimal metabolism and for reducing the hyperkalemia. As previously mentioned, rapid correction of the acidosis can cause a precipitous decline in the serum concentration of ionized calcium. Oral sodium bicarbonate or sodium citrate tablets are given to correct the metabolic acidosis, but intravenous sodium bicarbonate is used for patients who have severe acidosis or who cannot take anything by mouth.

Nutritional support is essential because the patients are in a highly catabolic state. This is particularly challenging in oligoanuric patients, who may be severely fluid restricted. Formula or parenteral nutrition should be concentrated whenever possible to provide maximum calories at a minimum volume. Children typically require only modest protein restriction (1–2 g/kg/day) and maintenance (or higher if catabolic) nonprotein calories. A low-phosphorous and low-potassium diet is also required. If adequate calories cannot be maintained because of fluid restriction, dialysis should be considered early in the course.[11]

Dialysis

The indications for initiating dialysis in AKI include

1. Volume overload unresponsive to conservative management
2. Hyperkalemia, acidosis, or hyperphosphatemia unresponsive to medical therapy
3. Uremia (mental status changes, serositis, or bleeding diathesis)
4. Nutritional support

The patient's overall condition must be considered before making a decision to start dialysis. This is also important when selecting the appropriate type of dialysis. One important consideration is the patient's hemodynamic status. Hypotensive patients are poor candidates for hemodialysis but are often suitable for peritoneal dialysis or continuous renal replacement therapy (CRRT).[21] There are no precise criteria for selecting a particular dialysis modality, and practice patterns vary widely. However, CRRT is rapidly becoming the preferred modality for pediatric patients with AKI in the intensive care unit (ICU) setting.[22]

CONCLUSION

The prognosis of a child with AKI is highly dependent on the underlying cause, the length of insult, the number of other organs involved, the amount of residual urine output, and whether dialysis is required.[23] The major complications of AKI include fluid overload, hyperkalemia, metabolic acidosis, hyperphosphatemia, hypocalcemia, and rarely uremia. Judicious management of these complications can vastly improve the morbidity and mortality associated with AKI in children. Immediate treatment of the underlying insult through fluid resuscitation in the case of prerenal injury or relieving the obstruction in postrenal injury can prevent the progression to intrinsic renal injury. Once intrinsic renal injury has been established, it is essential to maintain adequate renal perfusion while avoiding further nephrotoxic insults whenever possible. If medical management fails to control the fluid and metabolic abnormalities, dialysis may be necessary. The choice of which dialysis modality to employ primarily depends on the hemodynamic status of the patient. Recovery from intrinsic renal disease also depends on the underlying cause of the AKI. Children with acute interstitial nephritis or ATN typically recover normal renal function and are at low risk for long-term morbidity. Conversely, children who undergo a substantial nephron loss, as occurs in HUS, cortical necrosis, or RPGN, are at risk for the development of CKD long after the initial

insult. These children require lifelong monitoring of blood pressure, renal function, and urinalysis.

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CHAPTER 25

Renal Transplantation

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INTRODUCTION

Since the first human renal transplant in 1954, major advances in surgical techniques, organ donation, immunosuppression, and recipient care have dramatically improved outcomes.[1] Early transplants into pediatric patients resulted in high rates of morbidity and mortality, but in contemporary cohorts, pediatric patient and graft survival exceeds that of adults.[2] Approximately 700–800 renal transplants are performed in patients below the age of 18 in the United States each year, and currently, 989 pediatric patients are on the transplant waiting list.[3]

Although there have been many improvements in renal replacement therapy (RRT) with hemodialysis and peritoneal dialysis, renal transplant remains the gold standard treatment for patients with end-stage renal disease (ESRD). Transplant confers a significant survival advantage compared with those children who remain on the waiting list, reducing the risk of death by 75% at 2 years.[4] Children who undergo transplant also have been shown to have better growth parameters, social outcomes, and overall quality of life.[5,6] In fact, the final adult height of transplant recipients has been correlated with educational level, independent housing, paid activity, and marital life.[6] Renal transplant is cost-effective compared with chronic dialysis; however, lifetime costs remain high, on the order of $340,000 per patient.[7]

Many similarities exist between pediatric and adult transplantation, but special considerations must be made for children. There are differences in pathology leading to kidney failure, immunosuppression regimens, surgical techniques, and transition to adult care. Children also present a unique challenge due to longer life expectancy. This chapter reviews core concepts in pediatric renal transplantation, with a focus on urologic concerns among this unique group of patients.

PEDIATRIC CHRONIC KIDNEY DISEASE AND RENAL FAILURE

Chronic kidney disease (CKD) is the state of irreversible kidney damage causing a decline in renal function, substantial morbidity, and premature death. There are multiple definitions for CKD. CKD staging provided further clarification to allow an understanding of progression of disease (Table 25.1). Staging is also valuable in the follow-up of patients with congenital anomalies of the kidney and urinary tract (CAKUT) as a measure of the success of therapy. The Kidney Disease: Improving Global Outcomes (KDIGO) consortium defines CKD as any abnormalities of kidney structure or function with a glomerular filtration rate (GFR) of <60 mL/min/1.73 m^2 present for >3 months or with a GFR of >60 mL/min/1.73 m^2 with markers of kidney dysfunction (including proteinuria, albuminuria, renal tubular disorders, or pathologic abnormalities detected by history or imaging).[8] Stage 5 CKD, also called ESRD or kidney failure, refers to the state when the GFR drops below 15 mL/min/1.73 m^2. Children with ESRD have mortality rates that are 30 times higher than those without ESRD.[9] At this point, a patient must be referred for RRT or transplant evaluation.

The estimated incidence of pediatric CKD is 13.1 cases per million in the United States and 12–75 cases per million abroad.[10,11] The rate of CKD and ESRD is higher in boys due to an increased risk of CAKUT, including posterior urethral valves (PUVs), renal dysplasia, and prune belly syndrome.[12,13] Boys account for about 60% of cases of ESRD and subsequent renal transplants.

Underlying causes of CKD and ESRD originate from heterogeneous disorders that are distinct in children and adults. Whereas most cases of CKD in adults result from diabetes and hypertension, CAKUT disorders are the most common causes of CKD in pediatric patients who undergo renal transplant (Table 25.2). Overall, 45% of transplant recipients have a CAKUT diagnosis, including obstructive uropathy (21%), renal dysplasia or aplasia (18%), reflux nephropathy (8%), and polycystic kidney disease (4%). Patients with CAKUT can be affected with just one of these conditions, but they are more commonly found to have multiple issues along a spectrum. The remainder

TABLE 25.1 Chronic kidney disease stages

Stage	Estimated GFR (mL/min/1.73 m^2)	Prognosis
1	≥90	Normal GFR
2	60–89	
3A	45–59	Low risk of progression
3B	30–44	Intermediate risk of progression
4	15–29	High risk of progression and complications
5	<15	Kidney failure

Abbreviation: GFR, glomerular filtration rate.

TABLE 25.2 Primary diagnosis of renal transplant recipients

Primary diagnosis	*N*	%
Total	**11,182**	**100**
CAKUT	**5,038**	**45.0**
Renal aplasia/hypoplasia/dysplasia	1,769	15.8
Obstructive uropathy/PUVs	1,713	15.3
Reflux nephropathy	576	5.1
Polycystic disease[a]	339	3
Medullary cystic disease[a]	305	2.7
Prune belly syndrome	279	2.5
Denys–Drash syndrome[a]	57	0.5
Glomerular disorders	**3405**	**30.5**
Focal segmental glomerulosclerosis	1,308	11.7
Chronic glomerulonephritis	344	3.1
Congenital nephrotic syndrome	289	2.6
Familial nephritis	247	2.2
Idiopathic crescentic glomerulonephritis	195	1.7
Membranoproliferative glomerulonephritis—Type I	191	1.7
Pyelo- or interstitial nephritis	189	1.7
Systemic lupus erythematosus nephritis	172	1.5
Berger's (immunoglobulin A) nephritis	135	1.2
Henoch–Schonlein nephritis	115	1
Membranoproliferative glomerulonephritis—Type II	87	0.8
Wegener's granulomatosis	71	0.6
Membranous nephropathy	51	0.5
Diabetic glomerulonephritis	11	0.1
Other	**2,739**	**24.5**
Hemolytic uremic syndrome	288	2.6
Cystinosis	225	2
Renal infarct	144	1.3
Wilms' tumor	59	0.5
Oxalosis	58	0.5
Other systemic immunologic disease	34	0.3
Sickle cell nephropathy	16	0.1
Other	1,223	10.9
Unknown	692	6.2

Source: Adapted from North American Pediatric Renal Trials and Collaborative Studies 2014, Annual transplant report, https://web.emmes.com/study/ped/annlrept/annualrept2014.pdf (accessed February 20, 2017).

[a] Indicates diagnoses that may be present outside of the CAKUT spectrum.

of CKD cases result from glomerular diseases, like focal segmental glomerulosclerosis (11.5%), and acquired conditions, like hemolytic uremic syndrome (2.6%), renal infarct (1.3%), or Wilms' tumor (0.5%).[12] In one study, cases that progressed to ESRD occurred in 41% of patients with glomerular diseases and 29% with nonglomerular diseases.[14] Predictors of faster CKD progression were proteinuria, hypoalbuminemia, hypertension, dyslipidemia, and anemia.

Ultimately, a third of children with CKD who require RRT will be found to have a urologic abnormality, and 39% of children on the transplant waiting list carry a CAKUT diagnosis.[15] However, these disease processes are heterogenous, and primary diagnoses listed in reports may not provide enough information for precision in understanding the course of disease. There is potential for confusion and misclassification with the current system. For example, a patient diagnosed as "obstructive uropathy" may also have "aplasia, dysplasia, or hypoplasia" of the kidney. These categories, which are almost equally weighted, account for 30% of the pediatric patients undergoing transplant in the United States. Pre- and posttransplant course can vary dramatically depending on whether the dysplasia was related to obstructive uropathy. An attempt to decrease some of this confusion, including garnering a true understanding of the urologic causes of renal disease in children, may lie with the diagnosis of CAKUT. This broad term encompasses the majority of renal diseases involving the urinary tract and may allow us to better understand the ultimate course of the pediatric urologic patient with progressive CKD. Data from other countries that report suggest that patients with CAKUT comprise between 36% and 58% of patients with progressive CKD. The pediatric urologist has a pivotal role in the workup and management of a majority of these patients and may play a large role in the management after transplant.

PRETRANSPLANT EVALUATION

Medical Evaluation

Medical evaluation of children before renal transplantation is generally undertaken by a multidisciplinary team involving nephrologists, pediatric urologists, transplant surgeons, and other specialists as needed (psychiatrists, cardiologists, pulmonary or critical care physicians, etc.). There are several major requirements for the evaluation and preparation for renal transplant that have been shown to improve long-term outcomes and reduce complications.[2]

First, any contraindications to transplantation must be ruled out (Table 25.3). Absolute contraindications include active malignancy, systemic sepsis, multiorgan system failure, and irreversible extrarenal disease. Ongoing substance abuse and anticipated noncompliance are also contraindications that may be modifiable through work with a psychiatrist or social worker. Any active infections must be fully treated before immunosuppression can begin.

Next, human leukocyte antigen (HLA) matching must be performed, and any anti-HLA antibodies to the potential donor must be detected. Identical twin or sibling donors will have the best HLA match, but many pediatric patients will not have brothers or sisters available for organ donation. Therefore, most live donor allografts come from parents who will have a single haplotype match. This has implications for immunosuppression and tolerance induction.

TABLE 25.3 Contraindications to transplantation

Absolute contraindications
Malignancy (within 2 years)
Systemic sepsis
Multisystem organ failure
Severe untreated extrarenal disease (cardiopulmonary, neurologic, psychiatric, etc.)
Antiglomerular basement membrane antibodies (Goodpasture's disease)
Active substance abuse
Relative contraindications
Noncompliance
Lack of adequate social support
Severe malnutrition
Ongoing active infection
Rapidly progressive disease (i.e., hemolytic uremic syndrome)

The cardiovascular and nutritional status of patients is also important before transplantation. Many pediatric patients with ESRD are underweight and need aggressive nutritional support. Likewise, CAKUT patients can have urine-concentrating defects and fixed-urine outputs leading to large-volume fluid losses. Gastrointestinal access with a gastrostomy tube may be required for certain patients to achieve adequate nutritional intake, fluid balance, or medication administration.[16] Phosphate binders, vitamin D supplementation, and serum thyroid monitoring have been shown to prevent posttransplant bone disease.[17] On the other hand, weight control and prevention of obesity can reduce surgical and anesthetic risks, and mitigate weight gain after transplant.[18]

Routine immunizations must be completed prior to undergoing transplant. Vaccines protect from infectious diseases of childhood, but they may not be effective if administered to an immunocompromised patient. Antibody titer monitoring and booster doses may be required due to decreased immune responses in patients with ESRD.[2] Furthermore, live vaccines (especially varicella and measles) should be avoided in the setting of immunosuppression.[19] The influenza vaccine should be administered annually starting 6–12 months after transplant.

Hematologic evaluation includes a risk assessment of the transplant recipient for thrombotic complications. Vascular thrombosis accounts for 9.8% of graft losses.[12] Studies have identified several risk factors, including age of less than 2 years, hypercoagulable states like factor V Leiden or antiphospholipid antibodies, prior large-vein thrombosis, dialysis access thrombosis, and longer graft cold ischemia time.[20] If properly identified, patients with increased risk can be managed with anticoagulation prophylaxis and have outcomes comparable to those without risk factors.[21]

Finally, psychological and social issues must be considered. A systematic review found that 32% of patients had some degree of nonadherence to immunosuppressive regimens after kidney transplant, and 44% of graft losses were associated with nonadherence.[22] Most factors associated with nonadherence were socioeconomic (including lower income and lack of family support), psychological (including depressive symptoms or anxiety), and knowledge related (including confusion over regimens or poor communication with medical team). Preoperative education, counseling, and planning for strict follow-up protocols are required to ensure compliance and stability after transplant.[23] Social work involvement is also needed to ensure adequate insurance coverage is in place.

Urological Considerations

The high prevalence of urologic pathology in children with CKD and ESRD demands early urological evaluation and treatment. Abnormal urinary tract function can have a deleterious effect on kidney function, and intervention may be able to delay the need for transplantation. The goals of any pediatric urologist as part of a multidisciplinary team with nephrologists and transplant surgeons should be to optimize the bladder or appropriately reconstruct it prior to transplant and consider appropriate management of the native kidneys.[24] Workup generally involves serum chemistries, GFR estimation (with creatinine or cystatin C), functional urodynamic studies, cystoscopy to characterize any structural abnormalities, and renal ultrasound.

Currently, there are no guidelines for the best management of patients with CAKUT and progressive CKD. Limited data on progression and posttransplant outcomes are available, with few reported series directly comparing CAKUT outcomes with other causes of progressive CKD. There may be an opportunity for standardization and better assessment of pre- and posttransplant course when reviewing the CAKUT patients as a group. Pretransplant evaluation and management is not standardized, but many centers are employing a multidisciplinary approach to CAKUT patients. Identification of bladder dysfunction, upper tract anatomic abnormalities, urethral abnormalities, and vesicoureteral reflux (VUR) is important for successful long-term graft survival (Figure 25.1). The follow-up and treatment of these conditions, once identified, is variable.

Patients with neurogenic bladder dysfunction can have very high voiding pressures, abnormal storage volumes, and incomplete bladder emptying. Pressures of more than 40 cm of H_2O have been shown to have damaging effects on renal function through increased papillary pressure and intrarenal urine reflux.[25] Detrusor sphincter dyssynergia, secondary VUR, hydronephrosis, and chronic urinary tract infections (UTIs) all contribute to upper tract deterioration. Early workup with urodynamic studies focusing on compliance, leak point pressure, voiding pressures, and residual volumes, followed by aggressive bladder management with anticholinergics plus clean intermittent self-catheterization (CIC) and/or augmentation cystoplasty, can mitigate some of this potential damage.

Likewise, patients born with PUV can have lifelong bladder dysfunction, termed valve bladder, and a quarter will progress to ESRD.[26,27] Younger children exhibit high voiding pressures and low bladder compliance, which often necessitates a urinary diversion with a vesicostomy early in life or high-dose anticholinergic therapy with CIC.[28] Historically, undiversion was thought to be necessary

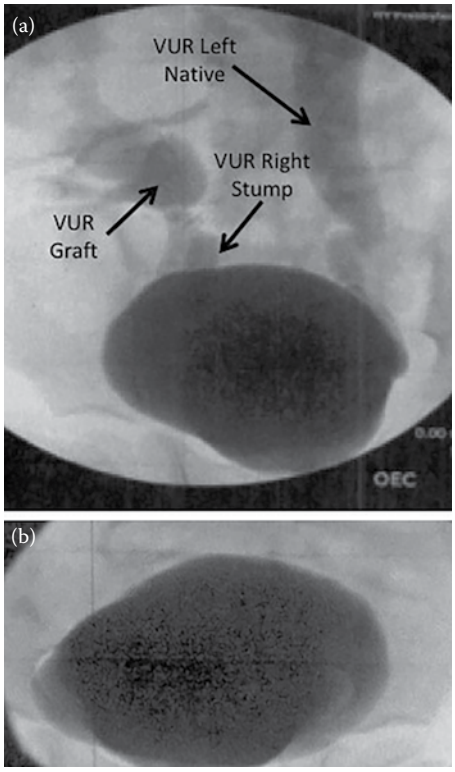

FIGURE 25.1 VUR after renal transplant. (a) Voiding cystourethrogram from a patient with three refluxing units after renal transplant. The patient had no urologic interventions performed before transplant, and the posttransplant course was complicated by delayed graft function and urosepsis. He underwent ureteroureterostomy to join the transplant ureter to the ureteral stump with simultaneous bilateral ureteral reimplantation of the native ureteral stump and left ureter. (b) Postoperative voiding cystourethrogram from the same patient with reflux is resolved.

prior to transplantation to evaluate bladder function and determine if there is a need for augmentation.[29] However, recent series have demonstrated the safety of transplanting a kidney into a diverted system.[30] Over time, severe polyuria and dysfunctional voiding can cause chronic bladder overdistension. Older children exhibit low voiding pressures and large bladder capacities, so efforts including timed voiding, CIC, and/or overnight catheterization should focus on maintaining a low postvoid residual volume to prevent urinary stasis and infections.[31] Pediatric urologists are critical to the care of these patients before, during, and after their transplants.

Risks and benefits should be weighed prior to performing an augmentation cystoplasty. The relationship between high intravesical pressures and transplant graft deterioration is well established, so augmentation is sometimes necessary to guarantee a low-pressure reservoir.[32,33] In several small case series, graft survival seems to be equivalent in patients with augmented bladders and those who have normal bladders.[34–36] Ileocystoplasty is the most common method of bladder augmentation, but risks include mucus production, bladder lithiasis, difficulty emptying, and metabolic acidosis. Alternatively, gastrocystoplasty can obviate some of these problems, but has different disadvantages, including hematuria or dysuria syndrome and rare alkalosis. The risk of malignancy is a concern for some, but is estimated to occur in <5% of cases.[37] Regardless, surveillance with cystoscopy and ultrasound is recommended beginning 10 years after augmentation.[38] Autoaugmentation and ureterocystoplasty were performed historically, but both techniques have fallen out of favor.[39] Augmentation can be performed either when the patient is ready for transplant listing or 6–12 weeks before a scheduled living donor transplant, prior to starting immunosuppression. For patients on peritoneal dialysis, it is important to realize that any transperitoneal surgery can compromise this approach by creating serosal disruptions and adhesions that will interfere with ultrafiltration. To avoid these adverse consequences altogether some urologists forgo augmentation of small-capacity bladders and have shown satisfactory outcomes with transplantation.[40]

The management of retained native renal units can also be a concern for urologists. Residual excretory capacity and erythropoietin production can provide physiologic benefit; however, issues like reflux and infection can present challenges.[41] Conflicting studies have suggested an increased incidence of UTI in patients with VUR.[42,43] The management of VUR in this setting is controversial, with options including observation, endoscopic bulking injection, ureteral reimplantation, and native nephrectomy. One study showed no difference in infection rate between observation and native nephrectomy, but decreased infections with reimplantation.[44] For high-grade reflux, reimplantation is preferred because it maintains the native ureters in case they are needed for future complication management with ureteroureterostomy or ureteropyelostomy.

Native nephrectomy is indicated for patients with persistent high-grade reflux, chronic renal infections (i.e., xanthogranulomatous pyelonephritis), infected renal stones, cystic disease, or refractory hypertension. Heavy proteinuria (>40 mg/m^2/h) can also merit native nephrectomy to eliminate protein loss and potentially decrease risk of thrombotic events.[41,45,46] Nephrectomy can be performed early, several weeks before transplant or simultaneously with transplant. However, some conditions, like xanthogranulomatous pyelonephritis or polycystic kidney disease, may make nephrectomy at the time of transplant too difficult or risky. When performing a nephrectomy before transplant, it should be approached from a flank or dorsal lumbotomy incision to account for the future transplant incision. For patients on peritoneal dialysis, a retroperioneal minimally invasive approach has been shown to preserve peritoneal integrity.[47] Finally, nephrectomy may reduce the risk of graft hypoperfusion by reducing organ steal and volume depletion from large native urine output.[41] The decision to perform native nephrectomy should be individualized with a discussion of potential risks and benefits of this strategy.

RENAL TRANSPLANTATION

When a patient becomes designated as stage 4 CKD with a GFR of <30 mL/min/1.73 m^2, it is time to start discussing potential RRT and possible renal transplantation.[48] The timing of deceased donor renal transplant (DDRT)

can be unpredictable. Living donor renal transplant (LRT) is more common in pediatric patients and confers certain advantages.

Deceased Donor

After revision of the kidney allocation policies in 2005 to prioritize organs from deceased donors of <35 years old to pediatric patients, the mean wait time decreased to 165 days or less from 360 days. Further changes to the Organ Procurement and Transplant Network (OPTN) kidney waiting list were put into effect in 2014, which now assigns points for pediatric patients, time on the wait list, sensitization, and quality of HLA match.[49,50] Currently, there are large geographic variations in waiting times for pediatric DDRT, which are associated with local organ donor supply and demand factors.[51] In 2015, 76% of all donor kidneys in the United States were from deceased donors.[15]

Organ donation from brain-dead individuals is coordinated by professionals on a local level, where evaluation, consent, and medical management are performed in a structured approach.[52] Organ retrieval is performed through a complete midline incision. After the aorta is flushed with cold preservation solution and the abdomen is packed with sterile saline ice slush, organs are sequentially removed, starting with the heart and ending with the kidneys. Kidneys are removed en bloc with adjacent aorta, vena cava, and ureters, which are divided at the bladder. They are then separated and prepared for transfer to their final destination.

While LRT is generally preferred over DDRT due to improved graft survival, deceased donor organs are preferred in certain cases where there is high risk for disease recurrence. For children with focal segmental glomerulosclerosis, 5-year allograft survival was comparable (60%–70%) for deceased donor and living donor organs.[53] In general, the best kidney for a child is one from a healthy teenager or young adult. Adult kidneys can be transplanted into children once they are more than 6.5 kg. Graft survival is low for deceased donors of less than 2 years old (51% 5-year survival) or more than 50 years old (58% 5-year survival).

Living Donor

Allografts from living donors have a significantly lower incidence of delayed graft function and better long-term graft survival than DDRT.[15] The failure rate at 5 years for LRT is 11.1% compared with 18% for DDRT. Notably, this advantage is lost when living donors are older than 55.[54] LRT allows for the planning of preemptive transplantation before the initiation of dialysis. Preemptive transplantation occurs in 25% of pediatric patients, as parents often try to avoid dialysis for their children.[12] This strategy has multiple advantages, including decreased cost, improved quality of life, prolonged graft survival, and improved overall survival.[55–58] One hypothesis was the ability to start immunosuppression early, but a randomized trial in 2003 showed that starting immunosuppression with cyclosporine and azathioprine before kidney transplant had no advantage over starting immunosuppression after.[59] Avoiding morbidity of vascular access and dialysis complications contributes substantial benefit.[58] Contraindications for preemptive transplant are active autoimmune disease, ongoing infection, need for transplant nephrectomy, and noncompliance.

Urologists are often involved in the workup and care of live kidney donors. Donors require a thorough history and physical exam, a psychiatric evaluation, and laboratory testing with blood typing, renal assessment, infectious screening, and malignancy screening. Donors must be reevaluated every 6–12 months to ensure continued medical and psychosocial suitability.[60] Since donation to a family member or altruistic donation can be fraught with emotions, informed consent with meticulous discussion of the risks of donation is critical. The most common postoperative complications are hematoma and abscess. The most serious long-term consequence for kidney donors is a 3.5–5.3 times elevated risk of developing ESRD, with even more risk for those with lower GFR, albuminuria, hypertension, current or former smoking, diabetes, and obesity.[61]

Living donor nephrectomy is often performed simultaneously with the exposure of the recipient. Alternatively, successful paired-exchange programs have been set up to increase access to living donors by facilitating simultaneous and nonsimultaneous organ swaps.[62,63] For the last 20 years, donor nephrectomy has been performed laparoscopically.[64] During the operation, particular care must be taken to preserve ureteral length by dissecting to the level of the bladder and to maintain blood supply, avoiding ureteral skeletonization. After the renal vessels are ligated, the kidney is extracted and flushed immediately with cold preservation solution. It is then placed in sterile saline ice slush and delivered to the recipient.

Close follow-up for the living donor is required due to these long-term risks. Some have advocated donor registries where these patients can be tracked. In cases where donors lose their remaining kidney due to trauma, cancer, or medical renal disease, they are given a very high priority on the OPTN kidney waiting list.[65]

Recipient Management

Children should be optimized immediately before transplantation. First, those with ESRD should undergo dialysis on the day of the transplant. Maintenance of appropriate volume status facilitates perfusion of the new graft.[66] Second, in multiple modern adult cohorts, immune induction therapy with antibodies targeting T cells (i.e., thymoglobulin, alemtuzumab, basiliximab, etc.) has been shown to decrease rates of acute rejection by one-third.[67] Despite mixed data in the pediatric literature, induction therapy is now routine practice in many pediatric patients, and specific protocols vary by medical center. Otherwise, patients require routine surgical preparation, including nothing to eat, vascular access, anesthesia consultation, and administration of prophylactic antibiotics.

For children more than 20 kg in weight, the pediatric renal transplant procedure is identical to that in adults—retroperitoneal exposure is achieved through an anterior, lower-quadrant "hockey stick" incision. Venous and arterial anastomotic sites along the common or external iliac artery and vein are identified. Overlying lymphatics

are divided between ligatures or clips to decrease the risk of postoperative lymphocele. After vascular control is achieved, venotomy and arteriotomy are made and venous and arterial anastomoses are sewn in place. Reconstruction of the renal vessels through spatulation, reanastamosis, and/or caval or aortic patches may be required due to variations in vascular anatomy. For young children less than 20 kg, a transabdominal approach can be utilized through a midline incision, and the kidney can be placed intraperitoneally with anastomoses to the aorta and vena cava.[2] In certain small children or when a small donor kidney is used, an extraperitoneal approach can be attempted, but it often requires closure of only the external layers, with delayed hernia repair. The new graft will immediately sequester 250–300 mL of blood, so maintenance of adequate blood pressures is essential to prevent posttransplant hypotension.[66]

Ureteral reimplantation can be performed directly into a native bladder (ureteroneocystotomy) using a transvesical "Leadbetter–Politano" technique or extravesical "Lich–Gregoir" technique. In a meta-analysis of two randomized trials and 24 observational studies, the extravesical Lich–Gregoir technique was favored due to reduced rates of anastomotic leakage and postoperative hematuria. Rates of ureteral stricture and incidence of VUR did not differ between techniques.[68] The Lich–Gregoir ureteral reimplantation also causes less discomfort and fewer bladder spasms.[69] Prophylactic stenting of the ureterovesical anastomosis is protective from major urologic complications (relative risk 0.24), including urine leak and obstruction.[70] The disadvantages of stent placement are an increased rate of UTI if the stent is left in place for more than 30 days and increased costs.[71] Some centers perform ureteroneocystotomy without stent placement unless there is an increased risk of urinary retention or high pressure.[72] Ureteroureteral anastomosis is an alternative reconstruction option in the setting of a small hypertrophied bladder, a very short transplant ureter, or a salvage procedure. A retrospective series of 23 patients showed acceptable outcomes with an 8% leak rate and no graft failures.[73] Regardless of approach, a Foley catheter is left in place postoperatively for 2–5 days.

POSTOPERATIVE CARE

Immediate postoperative care of transplant recipients can be complex and require coordination between multiple specialists. Daily clinical exam and monitoring of urine output, vital signs, and laboratories must be conducted. Special considerations are made for functional monitoring of the allograft, cardiovascular and respiratory support, fluid and electrolyte management, immunosuppression, and infection prophylaxis.

Monitoring fluid and electrolyte status is critical in the first days following surgery since hypotension can contribute to early graft loss. It is important to consider insensible losses from surgery and high urine output from a new kidney that cannot yet concentrate urine. Conversely, hypertension may occur in up to 80% of transplant recipients in the setting of fluid overload, steroid or calcineurin inhibitor treatment, donor factors, or renal artery stenosis. In the long term, elevated blood pressures can result in graft dysfunction, left ventricular hypertrophy, and death.[74] Calcium channel blockers are safe and effective for first-line therapy in the acute setting after surgery.

Pediatric immunosuppression regimens have rapidly evolved over the last 20 years with the introduction of induction antibodies that can downregulate immune response and the improved understanding of maintenance therapies. Immunosuppression is highest during the first 3–6 months after transplant, when the risk of acute rejection is highest, and then it is slowly tapered to maintenance levels. Ideally, adequate therapy is achieved while minimizing adverse effects, such as infection, nephrotoxicity, and malignancy. Outcomes of clinical trials and current protocols have been reviewed recently in the literature.[2,75]

Prophylaxis against infection is recommended in the initial months following transplant since infection is the leading cause of hospitalization and death after transplant.[76] UTI is the most common infection, occurring in 27%, and children with abnormal lower urinary tracts have increased risk.[77] Fortunately, UTI seems to have no effect on graft survival for patients on prophylactic antibiotics.[78] Antibiotic coverage with daily trimethoprim-sulfamethoxazole can prevent UTI and *Pneumocystis jirovecii* pneumonia. These children may benefit from lifelong antibiotic prophylaxis.

Infection with opportunistic viruses like cytomegalovirus, BK virus, Epstein–Barr virus (EBV), herpes simplex virus, and human immunodeficiency virus can cause graft dysfunction, complications, and even death. Prophylaxis from CMV with valganciclovir or ganciclovir significantly reduces infection and associated complications.[79] Screening and treatment of other opportunistic viruses with antiviral agents and modified immunosuppression regimens is detailed in the KDIGO clinical practice guideline for the care of kidney transplant recipients.[80]

COMPLICATIONS

Early Graft Dysfunction

Delayed allograft function is defined by the need for dialysis during the first week after transplant. Causes include acute ischemic injury, vascular thrombosis, surgical and urologic complications, and hyperacute rejection.[81] Delayed graft function occurs more frequently in DDRT (19%) than LRT (6%), and results in a six times greater risk of graft failure. Hyperacute rejection occurs within the first minutes of transplantation and is mediated by anti-HLA antibodies that activate the complement cascade against the allograft.[82] Acute rejection occurs in the days to months after transplantation and is defined by an acute deterioration in allograft function. Classic signs of acute rejection are fever and graft tenderness, but with modern immunosuppression, these signs are rarely found. Acute rejection is detected with a rise in serum creatinine and must be confirmed with graft biopsy. The rates of acute rejection are dropping—whereas rates in the late 1980s were 53% and 67% for LRT and DDRT, they are now 9% and 14%, respectively.[12] Although complete recovery from an acute rejection episode is possible, the likelihood

decreases with each subsequent episode. Patients with acute rejection have triple the risk of developing chronic rejection and loss of allograft over time.[83] Research is ongoing for new biomarkers to detect acute rejection earlier.[2]

Surgical Complications

Surgical and vascular complications are a major cause of graft loss. Wound complications are rare, but they can be devastating. Infection occurs in 2%–7% of cases.[84] Surgical site hemorrhage has been seen in 1%–5% of cases, and can result in significant blood loss, hematoma, and graft dysfunction or loss.[85] Spontaneous allograft rupture is a dangerous complication of transplantation, and occurs in 0.3%–3% of cases. Risk factors are acute rejection, acute tubular necrosis, and renal vein thrombosis, and salvage rates vary from 30% to 50%.[86]

Renovascular complications, including renal artery stenosis and vascular thrombosis, happen in 15% of cases.[87] Renal artery or vein thrombosis usually occurs within the first 3–5 days of transplant, and is the third most common cause of graft loss. Causes can be either technical (anastomotic defect or external compression) or nontechnical (young donor or recipient, low arterial flow, intimal injury, or hypercoagulability). Prevention of thrombosis through preoperative hematologic screening, anticoagulation prophylaxis, and hemodynamic monitoring was previously discussed.[21] Renovascular complications often require surgical revision, which can be performed with percutaneous angioplasty or primary repair.[88]

Urological Complications

Acute urological complications occur in 5%–22% of pediatric transplants.[72,87] Postoperative urinary obstruction and urine extravasation are the most common complications. Extravasation results from anastomotic leak, ureteral necrosis, or bladder injury, and is managed conservatively with stenting and bladder drainage or surgically with nephrostomy drainage, dilation, or reimplantation. Case series have shown that urological complications are not associated with donor type, preexisting urological pathology, surgical technique, or patient age.[72] Ureteral obstruction is more common in boys with PUV, but can also result from transient ureteral edema, anastomotic stricture, or hematuria with clots. In one case series, half of the patients with ureteral obstruction presented within 100 days of transplant, and 79% were found to have obstruction at the level of the ureterovesical junction.[89]

Urolithiasis can also affect transplant recipients. Stones are formed in 6% of adults and 1% of pediatric patients after transplant.[90] Diagnosis and treatment can be challenging since obstruction will not cause typical renal colic, and endoscopic access to a transplant kidney can be problematic. In the largest series of 20 patients, the presenting signs and symptoms were UTI (40%), hematuria (35%), dysuria or straining (45%), and asymptomatic (10%).[91] Risk factors identified included retained suture material, hypercalciuria, recurrent UTI, and urinary stasis. Other factors that contribute to stone formation in transplant patients are low urine output, alkaline urinary pH, hypomagnesuria, hypocitraturia, and hyperparathyroidism.[92] Stones can be treated with extracorporeal shock wave lithotripsy, retrograde ureteroscopy, or percutaneous nephrolithotomy, but comparative effectiveness data between these techniques are scant.

Postoperative VUR is noted in up to 58% of transplants.[93] If incidentally detected during screening or urodynamics, there appears to be no effect on graft survival.[72,94] However, if hydronephrosis and/or pyelonephritis develops, outcomes are worse.[95,96] Urologic disorders that predispose patients to transplant VUR include noncompliant bladder, detrusor overactivity, PUVs, or urethral stricture.[97] In certain cases with incompletely controlled bladder dysfunction, aggressive bladder management with anticholinergic pharmacotherapy and CIC can be enough to decrease urinary stasis and prevent renal damage. Endoscopic management with injection of collagen bulking agents has been attempted in transplanted kidneys with limited success.[98,99] Ureteral reimplant and/or submucosal tunnel lengthening has been shown to have success rates of almost 100%.[97] This procedure is performed in a small fraction (2%) of pediatric transplant recipients nationally.[100]

LONG-TERM FOLLOW-UP

After pediatric transplantation, the goal is to maintain allograft function and facilitate normal growth and development. Graft survival has dramatically increased with improved pretransplant preparation, better donor selection and matching, new immunosuppressive regimens, and posttransplant care pathways. One study of national trends in kidney transplant outcomes showed that each year since 1987 has conferred a 5% decreased hazard of graft loss, delayed graft function, and death.[101] Allograft survival is now 97% at 1 year, 78%–86% at 5 years, and 60%–78% at 10 years.[12] Long-term survival for children has consequently improved due to increased graft survival and decreased morbidity from surgery. According to the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) 2014 annual report, patient survival estimates for all patients at 1, 2, 5, 7, and 10 years posttransplant were 97.9%, 97.1%, 94.9%, 92.8%, and 89.9%, respectively.[12] Posttransplant survival is lowest in infants of <24 months old who receive deceased donor grafts, and they have a 3-year survival of 93.4%. LRT was associated with better survival (hazard ratio 0.79), whereas graft failure requiring dialysis was associated with much higher mortality (hazard ratio 4.85).[102] Those who lose a transplant graft must then compete with first-time candidates for subsequent DDRT and have higher rates of sensitization.[9] Some predict that modern transplants may last as long as 35 years, but these data have yet to mature.

The main causes of death in adults who have undergone renal transplantation are cardiopulmonary disease (15%) and infection (28%). Hypertension is common in up to 80% of recipients and is associated with chronic graft injury, decreased graft survival, cardiovascular complications, and mortality.[103] Furthermore, the rates of metabolic syndrome, diabetes, and left ventricular

hypertrophy all significantly rise after transplant.[104] Late graft failure usually results from chronic graft injury, calcineurin inhibitor nephrotoxicity, atherosclerosis, and recurrent renal disease (Table 25.4). Malignancy also contributes a substantial cause of death (11%). Immunosuppression is associated with development of malignancy. The overall malignancy incidence is 2.6%, with 84% developing lymphoproliferative disorders and 16% developing other cancers.[12] EBV-driven posttransplant lymphoproliferative disorder is the most common malignancy after transplant, and its prevalence has increased since the 1980s. Fortunately, due to earlier diagnosis and better therapies, survival has improved to 87% at 5 years from 48% in the 1990s.[105] Solid tumor risk is 6.7 times greater in pediatric transplant recipients than in the general population, and the most common tumor type is renal cell carcinoma.[106] As pediatric patients age, screening for preventable causes of death will become increasingly important.

Adolescents have been identified to be at very high risk during the transition period from pediatric to adult care due to high rates of nonadherence. As patients move toward increased autonomy and independence, issues arise, including missed clinic appointments, skipped tests, and medication noncompliance.[107] Rates are estimated between 5% and 50%, and nonadherence has been shown to be an important contributing factor for graft failure in teenagers.[22] Factors associated with poor adherence include older patient age, family stress or low family cohesion, patient psychiatric issues (distress, depression, or poor behavioral functioning), and poor patient knowledge. These findings underscore the need for new approaches, such as transition skills workshops and smartphone checklists to enhance compliance during this stage.[108]

TABLE 25.4 Causes of graft loss

Cause	N	%
Total	**3045**	**100**
Rejection	**1545**	**50.7**
Chronic rejection	1089	35.8
Acute rejection	396	13.0
Accelerated acute rejection	41	1.3
Hyperacute rejection	19	0.6
Vascular	**306**	**10.1**
Vascular thrombosis	291	9.6
Renal artery stenosis	15	0.5
Renal	**287**	**9.4**
Recurrence of original kidney disease	212	7.0
Primary nonfunction	65	2.1
De novo kidney disease	10	0.3
Other	**907**	**29.8**
Death with functioning graft	276	9.1
Medication noncompliance	133	4.4
Bacterial/viral infection	53	1.7
Malignancy	36	1.2
Other technical	34	1.1
Cyclosporine toxicity	13	0.4
Other/unknown	362	11.9

Source: Adapted from North American Pediatric Renal Trials and Collaborative Studies 2014. Annual Transplant Report [Internet]. web.emmes.com. https://web.emmes.com/study/ped/annlrept/annualrept2014.pdf (accessed February 20, 2017).

CONCLUSIONS AND FUTURE DIRECTIONS

Over the last 30 years, major advances in pediatric renal transplantation have been achieved. Improved understanding of pediatric renal pathology, the developing immune system, and surgical techniques has contributed to greatly improved graft and patient survival in the modern era. In the future, improved understanding of the genetics, developmental biology, and natural history of CAKUT disorders will contribute to improved treatment. Advances in immune modulation with tolerance induction have the potential to revolutionize organ transplantation and improve the quality of life for patients after surgery. Urologists have become critical members of the multidisciplinary care involved in the pretransplant, intraoperative, and posttransplant care of these pediatric patients. Evaluation and management of any urinary tract dysfunction is essential for the success of transplantation.

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CHAPTER 26

Renal Calculus Disease

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INTRODUCTION

The purpose of this chapter is to review the current knowledge of pediatric urolithiasis, with the emphasis being on the pathophysiology, clinical presentation, evaluation, and medical management of this condition. The surgical management of urinary calculi will be addressed in a separate chapter.

It is well established that pediatric urolithiasis is a distinctly different condition and is not as common as adult urolithiasis; however, there are quite a few similarities in the presentation and evaluation of this condition regardless of the age of the patient. Pediatric urolithiasis can be either a sporadic occurrence or an important manifestation of certain disease conditions with lifelong implications.

EPIDEMIOLOGY OF PEDIATRIC UROLITHIASIS

Children account for only 2%–3% of all patients with calculous disease.[1,2] Pediatric urolithiasis is endemic to certain developing countries and until recently was a relatively rare condition in the western hemisphere. *The incidence in the United States has been increasing over the past decade, possibly due to changing dietary and physical activity patterns in our pediatric population.*[3,4] There has also been a shift in the pathophysiology of the stones encountered in the United States. Previously, the majority of the stones were felt to be secondary to an identifiable underlying metabolic disorder.[5,6] Recent data, however, suggest that pediatric urolithiasis is evolving to a more adult-type pathophysiology, most likely due to changing dietary habits, increased incidence of childhood obesity, and lack of regular exercise in this age group.

Urinary calculus disease is more common in Caucasians, less commonly affecting those of African or Latin American heritage.[1] Boys and girls appear to be affected equally, despite earlier data suggesting a male preponderance.

The mean age at presentation is 6.9 years for girls and 5.2 years for boys.[7] Infected stones tend to occur more frequently in children under 4 years of age. *In the pediatric population, the rate of recurrence of stones is as high as 40%–70%*[8,9] and appears to be the highest for children with underlying metabolic risk factors.[8,10] *It is the high recurrence rate that prompts us to suggest that all children with stones undergo a metabolic evaluation.*

CLASSIFICATION

Several classification systems have been proposed to organize pediatric stone disease. The schema proposed by Smith is one of the most comprehensive and useful systems that we have encountered (Table 26.1).[88]

PATHOPHYSIOLOGY OF UROLITHIASIS

Formation of a stone in the urinary tract is a consequence of complex physical processes and represents the end manifestation of a multitude of diseases. The stone is produced as the culmination of many interrelated anatomic and physiochemical processes.[11] The major factors are supersaturation of lithogenic ions and crystallization of compounds in the urine (Figures 26.1 and 26.2). The formation of stones is influenced by urinary volume, pH, and the presence of urinary ions or compounds that function as promoters or inhibitors of lithogenesis (Figure 26.3).

The central event in calculus formation is supersaturation. If a urinary solute exceeds its solubility product (K_{sp} = a constant that is equal to the product of the concentrations of the pure chemical components at which the solid and the dissolved states are in equilibrium in water at standard conditions and temperature), crystallization of the solutes can occur. In normal individuals, urine is undersaturated. When a solute is added to a solvent, it dissolves in it until an equilibrium point is achieved (SS = 1). Beyond this point (i.e., between saturated and supersaturated states—*metastable zone*), no further dissolution is possible, but new nuclei do not form spontaneously.[12]

In normal urine, the concentration of a component necessary to reach supersaturation is several times higher than would be expected from its solubility because of the presence of naturally occurring organic and inorganic inhibitors that raise the K_{sp} of the urinary solutes (i.e., magnesium, citrate, pyrophosphate, glycosaminoglycans, nephrocalcin, and the Tamm–Horsfall protein).[13–17] Complexing agents are substances that form soluble complexes with specific crystals. Depending on the specific stone-forming substance, some chemicals, such as citrate and magnesium, may act as a complexor and/or an inhibitor.

Once urinary solutes exceed their K_{sp}, the solvent is said to be saturated (*unstable zone*) (Figure 26.1). Crystallization occurs via homogenous nucleation (on itself) or heterogeneous nucleation (on top of particulate matter, i.e., other crystals, cells, and tubular casts).

TABLE 26.1 Classification of urolithiasis in children

Enzyme disorders
• Primary hyperoxaluria (enzyme deficiency of)
• Type 1: Glycolic aciduria
• Type 2: Glyceric aciduria
• Xanthinuria (enzyme deficiency of)
• 1,8-Dihydroxyadeniuria
• Lesch–Nyhan syndrome (hyperuricosuria)
• Phosphoribosylpyrophosphate synthetase superactivity
• Orotic aciduria (enzyme deficiency of)
Renal tubular syndromes
• Cystinuria
• Renal tubular acidosis (Types 1–4)
Hypercalcemic states
• Hyperparathyroidism
• Immobilization
Uric acid lithiasis
Enteric urolithiasis
Idiopathic calcium oxalate urolithiasis
• Solute excess
• Hypercalciuria
• Absorptive
• Renal
• Hyperoxaluria
• Hyperuricosuria
• Medications excreted into the urine (sulfadiazine, indinvir, etc.)
Endemic bladder stone formation
Secondary urolithiasis
• Infection
• Obstruction
• Structural abnormalities
• Urinary diversion procedures
• Foreign body (ureteral stent, suture, etc.)

Source: Modified from Smith L, Segura J. *Urolithiasis*. Philadelphia: WB Saunders 1990:1327–52.

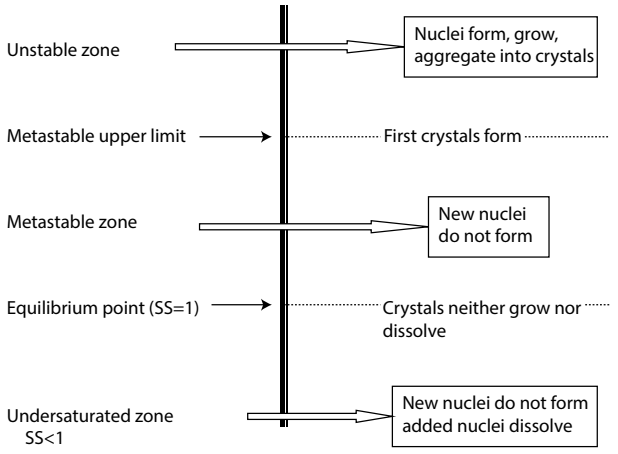

FIGURE 26.1 Urine is a complex solution and contains inhibitors and complexing agents that interact with other constituents, allowing a higher concentration of ingredients. After reaching a metastable upper limit, the solvent is said to be saturated (*unstable zone*) with the salt, and if more salt is added, if temperature and pH are unchanged, it crystallizes in the solution.

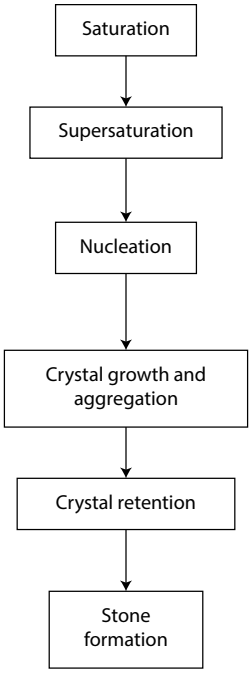

FIGURE 26.2 In urine, nuclei usually form through heterogeneous nucleation. Cells and other crystals can act as nucleating foci. Urine does not need to be continuously supersaturated for crystals to grow. If nuclei come in close contact and bind to each other (due to chemical and/or electrical forces), crystal aggregation starts.

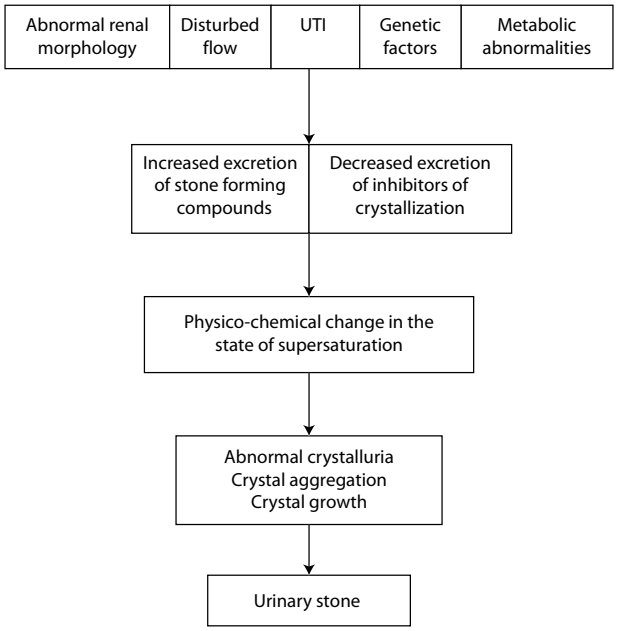

FIGURE 26.3 Renal, urologic, endocrine, and metabolic disorders may lead to the development of crystallized material in the urinary system. Abnormal renal morphology, disturbed urinary flow (obstruction, VUR, and neurogenic bladder), UTIs, systemic metabolic abnormalities, and predisposing genetic factors may all play a role in the increasing excretion of stone-forming constituents, crystal aggregation, and retention. The same factors may cause a decrease in excretion of inhibitors or complexing agents of crystallization.

In vivo, heterogeneous nucleation is much more common. Once this process is initiated, growth of the stone is fostered by the nuclei coming in close contact and binding to each other (due to chemical and/or electrical forces), resulting in crystal aggregation (Figure 26.2). Urinary pH influences the solubility of various lithogenic ions. Uric acid and cystine are more soluble in alkaline urine (pH >7.0).

Crystal retention and formation of calculi take place initially in the papillary duct. Disorders of metabolism, or endocrine or urological abnormalities may lead to the development of crystallized material in the urinary tract (Figure 26.3).

Any condition that results in urinary stasis (i.e., ureteropelvic junction obstruction or vesicoureteral reflux [VUR]) promotes the growth of a stone by increasing the excretion of stone-forming constituents, crystal aggregation, and retention, and a decrease in the excretion of inhibitors or complexing agents. It is very important to bear in mind that in reality, a combination of factors are involved in the genesis of urinary calculi.

CLINICAL PRESENTATION

The clinical manifestations of pediatric urinary stones are dependent on a number of factors:

- Size of the stone
- Location of the stone
- Degree of obstruction to the flow of urine
- Presence of infection
- Presence or absence of a normal contralateral renal unit

Presentation tends to be age dependent, with symptoms such as flank pain and hematuria being more common in older children. Nonspecific symptoms (e.g., irritability and vomiting) are more common in younger children.

Most symptoms related to urolithiasis occur when the calculus becomes lodged in the ureter, causing partial or complete obstruction. Typically, an obstructing calculus causes either renal colic and/or an infection. Renal colic, which occurs in approximately 40%–75% of children with urolithiasis,[9,18] presents with a sudden onset of severe cramp-like flank, abdominal, or pelvic pain associated with gastrointestinal symptoms (nausea and vomiting). Irritative voiding symptoms (i.e., dysuria, urgency, and frequency) occur when the calculus is in the distal one-third of the ureter. In some patients, the pain can present as diffuse abdominal pain and can obscure the clinical picture, delaying the correct diagnosis.[19]

Microscopic or macroscopic hematuria has been reported in up to 90% of children with urinary stones.[20]

Urinary tract infection (UTI) may complicate the clinical presentation, especially in an obstructed kidney, and may not be associated with acute renal colic, but rather persistent flank pain. The combination of flank pain and fever should immediately raise the suspicion for the presence of acute pyelonephritis occurring in the setting of an obstructed calculus, and this requires emergent intervention.

Children with urethral stones often present with terminal hematuria or the inability to void.

On physical examination, most children will be restless and costovertebral angle (CVA) tenderness may be elicited on the affected side. This presentation is less specific in younger children or renal transplant patients. Children under 5 years of age frequently present with symptoms suggestive of a UTI. Asymptomatic stones may be identified in children who are undergoing abdominal imaging for nonurological diagnoses (i.e., acute appendicitis).

EVALUATION OF THE PATIENT WITH UROLITHIASIS

History and Physical Examination

The initial evaluation of a pediatric patient with urolithiasis may suggest the diagnosis through a complete history and physical exam. The evaluation should begin with a review of the history and include questions regarding the following:

- Prematurity (especially with the use of furosemide), supplemental vitamin D, or enteral or parenteral nutrition formulas high in calcium and/or phosphorus
- Current medications (i.e., steroids, chemotherapeutic agents, diuretics, and protease inhibitors)
- Concurrent illnesses (i.e., cystic fibrosis, neoplasms, and seizures)
- Recurrent skeletal fractures, which could indicate the presence of hyperparathyroidism or other bone disease
- Nutritional habits (i.e., ketogenic diet, dietary excesses or deficiencies, and type and amount of fluid intake)
- Family history of nephrolithiasis, gout, or bowel disease

A wide variety of medical conditions can be associated with urolithiasis in children. These include gastrointestinal disorders resulting in malabsorption, chronic corticosteroid treatment, cystic fibrosis, myelodysplasia, and immobilization. The family history is helpful in patients with autosomal recessive disorders, such as cystinuria and primary hyperoxaluria, or with autosomal dominant diseases, such as renal tubular acidosis (RTA) or the syndrome of idiopathic calcium oxalate urolithiasis.

The physical examination should screen for chronic disease, including failure to thrive (distal RTA); hypertension as an indicator of underlying renal parenchymal injury; the characteristic bony deformities of rickets; photophobia due to band keratopathy (hypercalcemia-induced metastatic calcification); and evidence of UTI.

Imaging

The radiographic workup of a child with suspected urolithiasis is relatively straightforward. Recently, renal and bladder ultrasound emerged as the initial imaging modality of choice for children with suspected stone disease.[21,22] The current use of intravenous pyelography (IVP) is very limited in the pediatric population due to concerns about the risks of cumulative radiation exposure. Imaging

TABLE 26.2 Radiodensity of calculi on plain film imaging

Radiopaque calculi	Radiolucent calculi
Calcium oxalate	Uric acid
Calcium phosphate	2,8-Dihydroxyadenine
Struvite (carbonate Triamterene apatite)	Xanthine
Cystine	Silica

modalities, such as plain films of the abdomen (kidney, ureter, and bladder [KUB]), can be useful in detecting stones as well, and also suggesting the type of calculi (Table 26.2). *Calcium oxalate stones are usually less than 2 cm in size, whereas struvite, uric acid, or cystine stones may fill the entire collecting system, i.e., stag horn calculi.*

Currently, in both adult and pediatric stone patients, the unenhanced, helical computerized tomography (CT) scan is the "gold standard" technique for radiological evaluation of acute flank or abdominal pain.[23,24] It allows for an accurate and timely diagnosis of obstructed urinary calculi and can also detect extraurinary lesions.[25] CT scanners are readily available in most pediatric institutions and have the advantages of the brevity of the scan and avoidance of intravenous contrast (and any associated adverse reactions). At the same time, there are legitimate concerns about radiation exposure and lifetime risk of radiation-induced cancer.[26] Therefore, we recommend that the initial study for a child with a suspected stone be a renal bladder ultrasound.

Voiding cystourethrogram and renal nuclear scintigraphy may be necessary to rule out associated anatomical abnormalities in some patients. Children with suspected neurogenic bladder and significant voiding dysfunction might benefit from urodynamic studies, to complete their evaluation when dealing with chronic or recurrent urolithiasis.

Laboratory Evaluation

The evaluation of the patient may be divided into two phases—evaluation during an acute stone episode to direct therapy and subsequent evaluation to determine the underlying etiology of the stone. Owing to the high incidence of predisposing factors for urolithiasis in children (up to 75%), as well as the frequency of stone recurrences (up to 65%),[18] a complete evaluation of every child after the very first urinary stone is advisable.[27,28]

During the acute phase, the following tests are recommended:

- Urine for urinalysis and Culture and Sensitivity (C&S). (Urinalysis usually demonstrates hematuria, while pyuria may be a first sign of UTI, which is confirmed with a urine culture.)
- Serum electrolytes, blood urea nitrogen (BUN), and creatinine. (Determination of serum creatinine is helpful in grossly evaluating the renal function.)
- Complete blood cell count (CBC).
- Serum for Ca^{++}, phosphorous, magnesium, and Parathyroid hormone (PTH) levels may be useful in determining the type of stone being treated.

After treating the acute stone episode, it is of critical importance to collect a 24-hour urine sample in order to determine a stone risk profile and to rule out any subtle metabolic abnormalities.[9,29] The urine collection is evaluated for volume, pH, calcium, uric acid, creatinine, sodium, oxalate, citrate, and cysteine.

Supersaturation indices are felt to accurately predict stone composition, and they may be a more precise predictor of response to therapy.[30,31] We prefer two consecutive 24-hour urine samples as initial evaluation, ideally after the patient is free of stones. During the collection of 24-hour urine samples, the patient should maintain his or her usual diet and fluid intake. We use urinary supersaturation values as the principal laboratory benchmark index of possible crystal formation. Adult reference ranges for urinary supersaturation indices do not accurately reflect the pathophysiology in children.[32] We have shown that there are significant differences in the normal ranges of urine chemistries of children and adults (Table 26.3).[33] Calcium, oxalate, and citrate levels are significantly higher in children than adults when referenced by creatinine. Chemical analysis and determination of the composition of the stone (with polarization microscopy, infrared imaging, or x-ray diffraction) should be performed whenever possible. The patient should be given a urine strainer to retrieve any stones that are passed in his or her urine.

In the next section, we discuss the pathophysiology and specific treatment of the various types of stones encountered in children.

TABLE 26.3 Mean pediatric and adult urine chemistry values

Parameter	Pediatric	Adult	*P*-value
Urine pH	6.44 ± 0.40	6.05 ± 0.41	<0.001
SS Uric acid	0.59 ± 0.53	1.14 ± 0.99	<0.001
SS Ca oxalate	7.88 ± 4.13	7.85 ± 6.30	1.00
SS Ca phosphate	2.48 ± 1.31	1.42 ± 1.19	<0.001
Citrate/Cr (mg/g)	592 ± 460	373 ± 216	0.01
Oxalate/Cr (mg/g)	41.2 ± 26.7	23.1 ± 15.0	<0.001
Ca/Cr (mg/g)	172 ± 99	113 ± 55	0.001
Uric acid/Cr (mg/g)	623 ± 390	396 ± 89	0.01

Abbreviations: SS, supersaturation; Ca, calcium; Cr, creatinine.

Up to 90% of all pediatric kidney stones in the United States are composed of calcium oxalate; these stones are usually mixed calculi with some component of hydroxyapatite, or uric acid.[34,35] Around 5% of stones composed of struvite (magnesium ammonium phosphate) are usually encountered in the clinical setting of recurrent UTI. Less than 5% of stones are uric acid, brushite (calcium monohydrogen phosphate), or cystine.[35]

IDIOPATHIC CALCIUM OXALATE UROLITHIASIS

Hypercalciuria

Hypercalciuria is one of the most common predisposing metabolic factors for stone formation in children. Normal calcium excretion in children is less than 4 mg/kg/day. In general, children with a history of calcium oxalate urolithiasis excrete a higher fraction of dietary calcium in their urine than unaffected children.[18] Hypercalciuria is found in up to 50% of stone-forming children.[18,36] Microscopic or gross hematuria may be encountered in children with hypercalciuria without urolithiasis, although up to 20% of them will develop stones within 5 years.[37,38] Hypercalciuria has also been reported in association with the urinary frequency–dysuria syndrome.[39] Hypercalciuria is seen with a higher prevalence in children with Beckwith–Wiedemann syndrome and cystic fibrosis than in the normal population.[40] Initial studies of idiopathic hypercalciuria (normocalcemic hypercalciuria without an obvious etiology) suggested two relatively easily defined and genetically distinct subtypes of hypercalciuria, "renal" and "absorptive."[41] Some reports have postulated that absorptive and renal forms of hypercalciuria appear to represent a continuum of a single disease process.[42]

Absorptive hypercalciuria is by far the most common cause of excessive urinary calcium. It is due to one of the following causes of an increased intestinal absorption of calcium: overly aggressive vitamin D supplementation or excessive ingestion of calcium-containing foods (milk–alkali syndrome). Increased intestinal calcium absorption produces a corresponding increase in serum calcium levels. Typically, serum PTH is in the low–normal range in absorptive hypercalciuria because of feedback from the high-serum calcium level. Fasting urinary calcium levels are usually within the normal range in these patients.

Three types of absorptive hypercalciuria have been defined. *Type I* patients have hypercalciuria without calcium load. It is relatively uncommon and is the most severe type of absorptive hypercalciuria. *Type II* is the most common variety, where patients have hypercalciuria only with a high calcium intake. *Type III* is a relatively rare cause of hypercalciuria. In this condition, the underlying etiology is a renal defect that causes excessive urinary phosphate excretion. It is suspected to be due to an inactivation of the renal epithelial sodium-phosphate cotransporter—NaPi2. The continuous urinary phosphate loss rapidly depletes the serum phosphate level, causing hypophosphatemia. This results in an activation of vitamin D-3, which increases intestinal absorption of both phosphate and calcium. The absorbed calcium is ultimately excreted in the urine, causing the hypercalciuria.

Renal hypercalciuria is due to a specific defect in the kidneys that allows excessive obligatory urinary calcium excretion regardless of serum calcium levels, body stores, or calcium ingestion. The calcium-to-creatinine ratio is usually high (>0.20). The loss of serum calcium into the urine produces a mild hypocalcemia and secondary hyperparathyroidism, which is useful in diagnosing this condition. Renal leak hypercalciuria is far less common than absorptive hypercalciuria.

Hyperoxaluria

This condition is discussed in depth later in the chapter in the "Primary Hyperoxaluria" section. Up to 20% of patients with idiopathic calcium oxalate urolithiasis will have hyperoxaluria.[18] Oxalate has a very strong chemical affinity for calcium; calcium oxalate has a relatively low solubility. This is most frequently due to *idiopathic hyperoxaluria*, in which case urine oxalate values are only mildly elevated. It may be due to simple dietary excess of high-oxalate food sources or increased endogenous oxalate production. *In patients with enteric hyperoxaluria, calcium stones develop because of fat malabsorption, which in turn results in colonic hyperabsorption of ingested oxalate. The latter occurs because malabsorbed fatty acids bind luminal calcium, which is then unavailable to precipitate and prevent the uptake of ingested oxalate.*[43] Enteric hyperoxaluria is seen in patients with intestinal malabsorption or inflammatory bowel disease and may be treated with dietary adjustment and citrate supplementation.

Hyperuricosuria

Hyperuricosuria commonly occurs in patients with idiopathic calcium oxalate urolithiasis.[44,45] Hyperuricosuria may be the result of a diet high in purines or uricosuric drugs, or from tubular defects, such as an isolated defect in renal tubular urate reabsorption, or from generalized tubular dysfunction. It can also occur in patients undergoing chemotherapy with rapid cell turnover, and in those who are in a negative nitrogen balance (catabolic state). Hyperuricosuria leads to calcium oxalate crystallization by heterogeneous nucleation and by reducing the levels of urinary inhibitors.[46]

Hypocitraturia

Hypocitraturia is a common risk factor for urinary stone formation in patients with idiopathic calcium oxalate urolithiasis.[36,47] *Urinary citrate has a direct inhibitory effect on the crystallization and precipitation of calcium salts.* It binds to calcium ions in the urine, reducing calcium ion activity, which results in a lowering of the supersaturation of calcium phosphate and calcium oxalate. It also increases the inhibitory activity of other urine macromolecules (e.g., Tamm–Horsfall protein) and may reduce the expression of urinary osteopontin, which is an important component of the protein matrix of urinary stones. In addition, urinary citrate excretion can increase urinary pH, which negatively influences uric acid crystallization and uric acid stone formation. Citrate excretion is impaired by acidosis,

TABLE 26.4 Dietary recommendations for pediatric patients with calcium urolithiasis

Nutrient	Dietary recommendation
Fluid intake	Maintain urine output >2 L/day for adolescents and >20 ml/kg/day for younger children
Dietary sodium	No added salt diet (maintain Na <2 g/day)
Dietary calcium	Recommended daily allowance of calcium for age; avoid calcium restriction in children
Dietary protein	Recommended daily allowance; avoid excessive animal protein intake
Dietary potassium	Five servings per day of high-potassium, low-oxalate foods
Dietary phosphorus	Recommended daily allowance
Dietary magnesium	Recommended daily allowance

hypokalemia (causing intracellular acidosis), high-animal-protein diet (with an elevated acid-ash content), and UTI. Acidosis reduces urinary citrate by both enhancing renal tubular reabsorption and reducing the synthesis of citrate. *RTA is the most common cause of hypocitriuria in children.*

Medical Management

Since the single greatest risk factor of pediatric urinary stones is a low urinary flow rate,[48] *the management of all patients with metabolic stones starts with maintaining an adequate level of oral fluid intake even in young children.* One should strive to maintain a urine output greater than 2 L/day for adolescents and approximately 35 mL/kg/day for children.[49,50] Carbonated beverages are to be avoided and do not count as an appropriate oral fluid in these patients.

Calcium restriction in the growing infant, child, or adolescent should be avoided, as it only increases the risk for poorly mineralized bones. There appears to be widespread agreement that restriction of calcium intake contributes to the severity of a patient's osteopenia.[51,52] Individuals having elevated urine sodium–potassium ratios seem most responsive to the hypocalciuric effects of increased potassium intake in combination with a low-salt diet.[53] Dietary manipulations should initially be directed toward dietary excesses or deficiencies, and placing the child on a balanced and nutritious diet (see Table 26.4). The most frequently used medications to correct hypercalciuria are thiazide diuretics (1 mg/kg/day), which act to lower urinary calcium excretion by increasing the fractional calcium absorption by the distal nephron.[54] If RTA is suspected, potassium or sodium citrate is indicated, as it corrects the systemic acidosis, hypercalciuria, hypocitraturia, and hypocalemia.[55] Children with Type III absorptive hypercalciuria (phosphate leak) may benefit from treatment with orthophosphates.[56] Patients with urolithiasis secondary to a ketogenic diet need to be managed in close consultation with their neurologist, as these patients are on a very strictly regimented diet, in terms of volume and caloric intake.[57]

HYPERCALCEMIC STATES

Hyperparathyroidism

Resorptive hypercalciuria is due to the loss of calcium from the body's normal stores in the bony skeleton and is typically diagnosed in children with hyperparathyroidism. Although primary hyperparathyroidism is not a common cause of hypercalcemic hypercalciuria in children, it must be considered in a patient with elevated serum calcium.[58] In this condition, calcium is released from bone in response to the increased activity of osteoclasts caused by excessive and inappropriate serum PTH levels. This causes significant hypercalcemia. *Under normal conditions, PTH causes the kidney to limit calcium excretion, but with the overwhelming serum calcium load produced with hyperparathyroidism, the kidneys are forced to excrete the extra calcium into the urine, resulting in hypercalciuria.*

Immobilization

Immobilization of children is the most common cause in North America of secondary hypercalciuria.[7] The patients primarily at risk are those acutely immobilized for the management of fractures, postoperative management, as opposed to those with static neurological disorders who are chronically bedridden (i.e., spastic quadriplegia).

Others

Gastrointestinal hyperabsorption can be secondary to symptomatic vitamin D intoxication characterized by failure to thrive, anorexia, polyuria and dehydration, and variable degrees of renal insufficiency. The hypercalcemia of sarcoidosis is due to excessive $1,25(OH)_2$ D3 production by alveolar macrophages and in sarcoid granulomas. In the management of these conditions associated with hypercalcemia, it is critical to identify the underlying cause and correct it.

URIC ACID LITHIASIS

Uric acid calculi are radiolucent and comprise up to 5% of the urinary calculi encountered in pediatric patients. These stones are usually white or orange. *Uric acid crystals are orange and can often be mistaken for blood by the patient or their parents.* A pH below 5.8 promotes uric acid crystal precipitation since they are poorly soluble in acidic urine. In the familial, or *idiopathic*, form of the disease, affected children have *hyperuricosuria* and normal uric acid serum concentration. Generalized dysfunction of tubular reabsorption, as seen in patients with Wilson's disease, or various forms of the Fanconi syndrome are associated with familial hyperuricosuria.

Disorders associated with *overproduction of uric acid* include inborn errors of metabolism, such as Lesch–Nyhan syndrome and Type I glycogen storage disease (glucose-6-phosphatase deficiency).[59] Uric acid overproduction can also occur secondary to myeloproliferative disorders (presenting acutely or in relapse), or other causes of cell breakdown (catabolic states induced by neoplasms or chemotherapy). Hyperuricosuria may be the result of a high purine intake or uricosuric drugs (such as probenecid or salicylate) or from tubular defects, such as an isolated defect in renal tubular urate reabsorption, or from generalized tubular dysfunction.[60] Chronic diarrhea1 syndromes (e.g., ulcerative colitis and regional enteritis) or jejunoileal bypass surgery may cause uric acid lithiasis by inducing a net alkali deficit and lowering urine volume (thereby reducing urinary pH and augmenting urinary concentration of uric acid, respectively).[61] The majority of patients with hyperuricosuria have coexistent hypercalciuria; therefore, calcium oxalate urolithiasis may be seen in these children as well.[44]

Since most of these patients have a low volume of chronically acidic urine throughout the day, increasing oral fluid intake and urinary alkalization to a pH of 6.5–7.0 with potassium citrate or sodium bicarbonate are the primary goals of treatment. However, alkalinization of the urine above pH 7.0 can promote calcium phosphate stone formation. Patients with hyperuricemia secondary to myeloproliferative disorders may benefit from decreasing uric acid production with the xanthine oxidase inhibitor allopurinol. A rare complication of prolonged allopurinol therapy is the formation of xanthine stones.[62]

RENAL TUBULAR SYNDROMES

Renal tubular acidosis

RTA is a term applied to several clinical syndromes of metabolic acidosis that result from specific defects in renal tubular hydrogen ion secretion and urinary acidification. Three major types are currently recognized and are differentiated based on the nature of the tubular defect. Stones are composed principally of calcium phosphate (brushite), although calcium oxalate and struvite stones may be seen alone or in combinations.

In *Type 1 (distal) RTA*, the primary functional abnormality is the inability of the distal nephron to establish and maintain a hydrogen ion gradient between the tubular fluid and the blood. As a result, the urine remains inappropriately alkaline regardless of the severity of the systemic acidemia. Type 1 RTA is associated with renal stone disease in up to 70% of cases. Factors contributing to stone formation include increased urinary pH, hypercalciuria, and hypocitraturia.[63,64] Obstructive uropathy is an example of an etiology of distal RTA.

In *Type 2 (proximal) RTA*, the primary defect is a failure of bicarbonate reabsorption in the proximal tubule leading to bicarbonate wasting. However, the kidney is able to acidify the urine appropriately and to excrete the daily load of acid, as distal tubular function is spared. Nephrolithiasis and nephrocalcinosis are not seen in proximal RTA.[63]

In *Type 4 RTA*, chronic renal parenchymal damage leading to moderate reductions in glomerular filtration rate produces hyperkalemic, hyperchloremic metabolic acidosis in conjunction with bicarbonaturia, decreased ammonium excretion, and subnormal net acid excretion.[63] Nephrolithiasis and nephrocalcinosis are absent in Type 4 RTA.

Type 1 RTA may present as an isolated entity, or it may be the secondary manifestation of a variety of systemic and renal disorders, including Sjögren's syndrome, Wilson's disease, and primary biliary cirrhosis, and in patients who have undergone a jejunoileal bypass. Children usually present early with familial (autosomal dominant) Type 1 RTA. Infants generally present with vomiting and/or diarrhea (>33%) and failure to thrive (>50%), with subsequent growth retardation. Less than 10% have nephrolithiasis and nephrocalcinosis. Children present with metabolic bone disease (osteomalacia) or with signs and symptoms related to stone disease.

Patients with Type 1 RTA will present with a hypokalemic, hyperchloremic metabolic acidosis. In these patients, their urinary pH will never fall below 5.5 no matter how low the serum bicarbonate level.[63] Hypocitraturia and hypercalciuria will only be found in Type 1 RTA, but they are not specific for this disorder. A diagnostic workup for the presence of incomplete distal RTA is indicated when nephrocalcinosis or recurrent nephrolithiasis of unclear etiology occurs in the absence of spontaneous, nonanion gap acidosis. While these patients do not have spontaneous metabolic acidosis, they are unable to acidify the urine appropriately when presented with an acid load.[65] This condition is diagnosed by means of an ammonium chloride loading test and monitoring the urine pH. If at any time the urinary pH falls below 5.5, the diagnosis of RTA can be excluded.

Cystinuria

Cystinuria is a complex autosomal recessive disorder, characterized by an abnormality in a specific transport system located in the brush-border membrane of the proximal straight renal tubule and the small intestine. The transporter (SLC3A1 dibasic amino acid transporter) is encoded on chromosome 2p21. Cystinuria results from an excessive urinary excretion of cystine (the disulfide dimer of cysteine) and the dibasic amino acids arginine, lysine, and ornithine.[66,67] Cystine has poor solubility in the normal urinary pH range, and a pH below 7 causes cystine to precipitate. Cystine stones are usually very hard and resistant to fragmentation by extracorporeal shock wave lithotripsy (ESWL).

There are three subtypes of cystinuria, and it occurs with a frequency of 1 in 15,000 live births[68,69] and accounts for 1%–5% of children with metabolic urolithiasis in industrialized countries.[7,35] Cystine crystals are characteristically flat, hexagonal, and colorless. Cystine crystals are diagnostic, but are detected in only 19%–26% of homozygous cystinuric patients.[66] Cystinuria has been associated with hyperuricemia, uric acid urolithiasis, hemophilia, retinitis pigmentosa, muscular dystrophy, muscular hypotonia, mental retardation, trisomy 21, and hereditary pancreatitis.

The treatment goals of this condition include maintaining a high fluid intake to reduce cystine saturation (the goal is less than 300 mg cystine/L of urine), with urinary flow rates of up to 50 mL/kg/24 hours.[70,71] Further reduction of cystine concentration can be achieved with a diet low in protein and sodium. Urinary alkalization with potassium citrate at a pH of approximately 7.6 should be maintained in all patients. In children in whom hydration and alkalization have failed, D-penicillamine (20–50 mg/kg/day) and/or alpha-mercaptopropionyglycine (Thiola) (15 mg/kg/day) can be effective in decreasing the rate of stone formation. These drugs can be associated with serious side effects, and patients taking them must be monitored very closely for bone marrow suppression, nephrotic syndrome, and complications resembling systemic lupus and Goodpasture syndrome. Thiola has been reported to be better tolerated by pediatric patients. Vitamin B-6 supplementation must be added for patients being treated with either medication. Captopril has also been shown to be effective in lowering the urinary cystine level in homozygous cystinuric patients, by forming a thiol-cysteine mixed disulfide compound that is more soluble in urine than cystine.[72] Patients with cystinuria are at a very high risk for recurrent urolithiasis.[73,74]

ENZYMATIC DISORDERS

Primary Hyperoxaluria

This is a very rare but serious disorder caused by a congenital defect resulting in very high levels (>200 mg/day) of endogenous oxalate production.[75] Without treatment, the prognosis for these patients is poor. Renal failure occurs in 50% of patients by age 15 years and in 80% by age 30 years. Standard dialysis for uremia cannot remove enough serum oxalate to protect the kidneys and other organs from widespread calcium oxalate deposition (i.e., oxalosis) and calcium oxalate stone production.

Type I hyperoxaluria is the more common variety. It occurs in 1 per 120,000 live births and is transmitted as an autosomal recessive trait. It is caused by a deficiency of the peroxisomal liver-specific alanine–glyoxylate aminotransferase enzyme (i.e., *AGT*). Pyridoxine (vitamin B-6) is a cofactor in this chemical pathway, which normally converts glyoxylic acid ($C_2H_2O_3$) to glycine. When the pathway is blocked because of a deficiency or absence of this enzyme, it results in high levels of glycolic and oxalic acid, which are readily converted to oxalate that is then excreted in the urine.

The median age for presentation of initial symptoms related to hyperoxaluria is 5 years. Oxalate deposition can occur in other organs (e.g., bones, joints, eyes, and heart). In particular, bone tends to be the major repository of excess oxalate in patients with primary hyperoxaluria. Bone oxalate levels are negligible in healthy subjects. Oxalate deposition in the skeleton tends to increase bone resorption and decrease osteoblast activity. Because of the clinical variability, the diagnosis is often overlooked and only realized after the loss of a transplanted kidney.[76] Symptoms occur relatively late and are associated with very serious complications; screening all pediatric patients who have stones for hyperoxaluria is important. Discovering this condition may allow earlier testing, detection, diagnosis, and preemptive therapy in affected siblings.

Type II hyperoxaluria is much less common than Type I hyperoxaluria and is due to a deficiency of D-glycerate dehydrogenase (DGDH). This deficiency promotes the conversion of glyoxylate to oxalate. The degree of hyperoxaluria is approximately the same between the two types of primary hyperoxaluria. End-stage renal disease is slightly less common in patients with this form of primary hyperoxaluria than in those with Type I hyperoxaluria.

Primary hyperoxaluria requires vigorous management and careful follow-up. Therapy includes promoting a high urinary flow rate around the clock, and restricting dietary oxalate. Restriction of dietary calcium can result in increased oxalate absorption via the gastrointestinal tract and should be avoided.[20] Pyridoxine supplements (25–250 mg daily) have been shown to lower oxalate production and decrease the need for renal–liver transplantation.[77] Pyridoxine is generally not effective in patients with Type II primary hyperoxaluria.

Curative treatment involves a combined kidney and liver transplantation. Renal transplantation alone is insufficient because the liver defect causing the hyperoxaluria is not corrected. In selected patients, an early liver transplantation prior to the development of overt renal failure may preserve the native kidneys, thus avoiding the need for renal transplantation.

Xanthinuria

Xanthinuria is a descriptive term for excessive urinary excretion of the purine base xanthine. The two inherited forms of xanthinuria result from a deficiency of the enzyme xanthine dehydrogenase, which is responsible for degrading hypoxanthine and xanthine to uric acid. The resultant increase in plasma levels and excess urinary excretion of the highly insoluble xanthine, leads to urolithiasis, arthropathy, myopathy, crystal nephropathy, or renal failure.[78] More than half of the xanthine uroliths occur in children younger than 10 years. Iatrogenic xanthinuria can occur during allopurinol therapy, which is used to reduce urine uric acid excretion in conditions with endogenous overproduction of uric acid. Inhibition of xanthine dehydrogenase by allopurinol may lead to accumulation and urinary excretion of xanthine. No specific therapies are available for classic xanthinuria.

Lesch–Nyhan Syndrome (Hyperuricosuria)

The enzymatic defect associated with Lesch–Nyhan syndrome is a deficiency of the enzyme hypoxanthine-guanine phosphoribosyl transferase (HPRT).[79] HPRT normally plays a key role in the recycling of the purine bases, hypoxanthine and guanine, into the purine nucleotide pools. In the absence of HPRT, these purine bases are degraded and excreted ultimately as uric acid. In addition to the failure of purine recycling, the rate of synthesis of purines is markedly increased, presumably to compensate for purines lost by the failure of the salvage process.

This is a genetic disorder associated with overproduction of uric acid, neurological disability, and behavioral problems. The overproduction of uric acid is associated with hyperuricemia. If left untreated, it can produce nephrolithiasis with renal failure, gouty arthritis, and solid subcutaneous deposits known as tophi. The neurological disability encompasses a spectrum of extrapyramidal signs, including dystonia, choreoathetosis, and occasionally ballismus. The behavioral problems include cognitive dysfunction, aggressive and impulsive behaviors, and self-mutilation.

The majority of patients present between 3 and 12 months of age with delayed motor development, most commonly hypotonia or failure to reach normal motor milestones. A smaller number of patients present with complications related to the overproduction of uric acid. Sometimes the parents give a history of "orange sand" in the diapers, which is caused by uric acid crystalluria and microhematuria. Other patients may present with renal failure or frank hematuria, resulting from nephrolithiasis. The control of uric acid requires allopurinol, which inhibits the metabolism of hypoxanthine and xanthine to uric acid by the enzyme xanthine oxidase. Generous hydration at all times is essential. Hydration should be increased during periods of increased fluid loss, such as a febrile illness or recurrent emesis.

INFECTION STONES

Infection-related stones constitute about 2%–3% of the stones in pediatric patients and most commonly are seen in younger children (less than 6 years of age). *Infection by urea-splitting bacteria results in increased urinary pH (large amount of NH_4) and increased urinary magnesium ammonium phosphate, conditions favoring the formation of struvite stones.*[80] A urinary pH of 6.8 or more results from the action of the bacterial enzyme urease on the urinary urea. The resultant stones (which have a tendency to grow rapidly and form stag horn calculi) are intrinsically contaminated by bacteria, and the affected children all have findings of persistent pyuria, bacteriuria, and struvite crystalluria. More than 45 types of microorganisms are capable of urease production. *Proteus* species are isolated in more than 70% of all patients with infected stones, although *Pseudomonas*, *Klebsiella*, *Streptococcus*, and *Mycoplasma* species may also produce urease.[81]

To treat struvite stones successfully, the stone harboring the infection should be eliminated completely. In such cases, antibiotics alone cannot reach microorganisms and urinary infection recurs as soon as antibiotics are withdrawn. Select patients will benefit from hemiacidrin irrigation, which can dissolve some struvite stones. Acetohydroxamic acid (AHA), a urease inhibitor, is available for the management of stones caused by infection.[82] Genitourinary tract abnormalities predispose to the formation of infected stones (most frequently by obstruction); therefore, careful urological evaluation of the patient with infected stones is mandatory.[34] Findings of obstruction or a structurally anomalous urinary tract in these patients do not obviate the need for careful metabolic assessment. In one study of 66 patients with structural anomalies of the urinary tract, 36% had coexistent metabolic abnormalities. In the same study, of the 41 patients with infection-related stones, 56% had genitourinary anomalies and 29% had metabolic abnormalities.[18]

MISCELLANEOUS STONES

Triamterene Stones

Triamterene is a potassium-sparing diuretic. Seventy percent of the orally administered medication appears in the urine. One in 1500 patients on this medication will develop stones.[83]

Sulfadiazine Stones

Sulfadiazine is a medication that is used to treat toxoplasmosis in patients with HIV. Sulfadiazine crystalluria occurs in up to 49% of the patients treated with this medication. The exact incidence of this medication causing stones is unknown. Most sulfadiazine stones are radiolucent. Treatment includes hyperhydration and alkalinization of the urine.[84]

Indinavir (Crixivan) Stones

Indinavir is a protease inhibitor and is used as an antiviral drug in the treatment of HIV. Twenty percent of the administered medication is excreted unchanged in the urine. Patients who do not maintain a urine output of >1.5 L/day while on this medication will often have crystalluria and occasionally develop indinavir stones.[85] Stone development occurs at a higher urine pH (>6.0). These stones are typically radiolucent, and composed of a soft yellowish-brown gelatinous material. Unenhanced CT imaging may fail to demonstrate these stones, and a high degree of suspicion should be maintained in patients at risk for these stones.[86] Due to their soft nature, ESWL is often not useful in treating these stones, but they do respond to hyperhydration and mechanical removal of the stone (i.e., stone basketing).[87]

SUMMARY

Urolithiasis in the pediatric population has diverse etiologies and presentations. With a careful and systematic evaluation of the patient and individualized management strategies, recurrent stones, renal injury, and patient morbidity can be minimized. Once again, we would like to emphasize that the adult urinary values for the metabolic stone risk profile are not accurate for use in pediatric patients.

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CHAPTER
27

Endourology for Stone Disease

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EPIDEMIOLOGY

Over the past three decades, pediatric urologists have noticed a change in the epidemiology of pediatric urolithiasis, with transition from lower to upper tract stones, along with a rise in the incidence.[1] Both hospital admissions and population-based records seem to support this trend, although the etiology for the rise in stone incidence is not well defined.[2–4] Prior to 1990, urolithiasis was responsible for 1 in 1000 to 1 in 7600 hospital admissions annually throughout the United States.[5] Newer data derived from the Pediatric Health Information System (PHIS) database indicate that pediatric stone disease accounts for 57 per 100,000 (1 in 1,754) children seen annually at representative children's hospitals.[4] The public health impact of pediatric stones can no longer be ignored as a contributing factor to the $2.1 billion annual cost of urolithiasis.[6] Bush and colleagues found that pediatric stone disease accounted for 1 in 685 hospital admissions annually,[3] with regional variation among hospitals. Additionally, retrospective series from industrialized countries, including the United States, the United Kingdom, and Iceland, have echoed concern for a higher than expected incidence of pediatric stone disease.[7–9] The Icelandic series estimates an incidence of 5.6 per 100,000 children, most of which had metabolic abnormalities.[8] Studies from the United States also report frequently finding metabolic abnormalities during stone workup.[10] A 2003 study from the United Kingdom compared 5-year periods from the late 1960s to the late 1990s, noting a decline in infectious stones offset by a rise in metabolic-induced stones in children (Figure 27.1). Finally, a 40-year review from Japan revealed a rising incidence of urolithiasis in children and adults of all ages.[11]

ETIOLOGY

There appears to have been a stage migration from bladder stones to upper tract stones[12] of predominantly calcium content,[12–14] with concern that this is occurring as more countries adopt a Western diet high in salt and processed foods, with less water drinking. Endemic areas, such as Pakistan and Turkey, have previously estimated the prevalence of pediatric stones, including bladder stones, at 15% of children.[15] For such countries with endemic stone disease, the consequences are severe, accounting for 8% of cases of end-stage renal disease.[16] North American data suggest that predialysis urolithiasis is a more frequent occurrence than in age-, race-, and gender-matched adults, with an 8.3% prevalence compared with 2.6% in the general population.[17]

The incidence and prevalence of pediatric stone disease is consistently different by country. It seems unlikely that this rising incidence is secondary to poor diet or better detection, although both are certainly regional factors. Different cultures will have different stone types and patient demographics as an underlying pattern,[18] and many countries have reported that these patterns are changing over time. Adolescent females form a particularly at-risk subset for upper tract stone disease, whereas males often present in the first decade of life[19–22] (Figure 27.2). Studies evaluating differing hormone profiles by age and gender are not available in children, so the etiology for this difference is unclear. A few reports have attempted to link body mass index to risk of stone formation in children,[9,23] as obesity has tripled among U.S. children since the 1980s.[24] Analysis of urinary metabolites has shown higher rates of hyperoxaluria, hypocitraturia, and hyperuricosuria in obese children.[23,25] However, recent data refute a positive association of stone disease with obesity.[19,26,27] Further metabolic data exist to suggest that the rise in pediatric urolithiasis is due to factors other than obesity. Citrate levels and urine pH appear to be fairly constant when stratifying pediatric weight by adult BMI cutoffs,[28] and many researchers agree that calcium excretion appears more closely linked to dietary sodium and protein than obesity.[25,28] Hydration, fluid status, and consumption of sweetened beverages may contribute to rising stone disease in children, as beverage consumption transitions away from water and milk to soft drink consumption.[29–31] Dietary and lifestyle evolution likely play large roles, although environmental factors may contribute to rising stone disease. Brikowski and colleagues have offered mathematical models suggesting that stone prevalence will increase in the United States as annual temperatures rise due to cyclical variation or global warming, although this theory remains as yet unsubstantiated with clinical data.[32] Finally, one cannot discount the potential that stone diagnoses are more commonly made incidentally with the widespread availability of highly sensitive radiographic imaging, namely, noncontrast computed tomography (CT) scans. For example, the performance of CT scans for nephrolithiasis evaluation has increased almost 20% between 1999 and 2008.[4]

Certain cultures or geographic regions are known to have characteristic stone types, which may alter the selection of radiographic imaging, threshold for imaging,

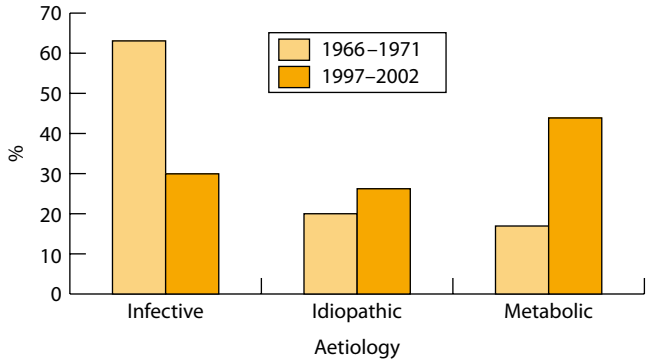

FIGURE 27.1 Data from the United Kingdom demonstrating a shift in the type of pediatric stone disease for the modern era, including a decline in infectious stones with a rise in idiopathic and especially metabolic-related calculi. (Reproduced from Coward R et al. *Arch Dis Child* 2003;88:962–5. With permission.)

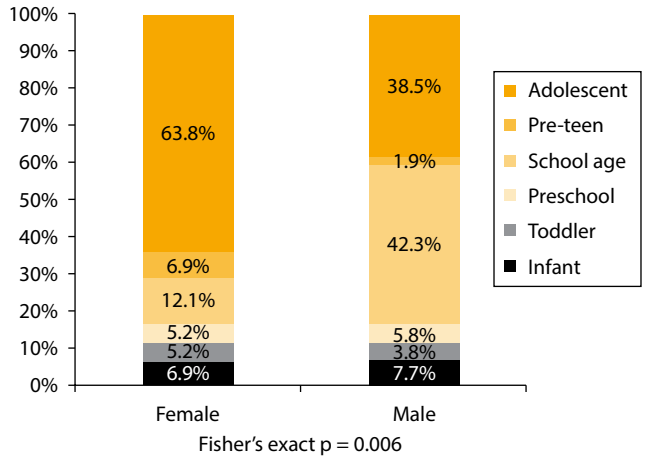

FIGURE 27.2 Data from the Children's Hospital of Philadelphia insurance records indicate a significant difference in the age of presentation for male vs. female children. Male children overall have a younger age at presentation, compared with female children, who often present during adolescence. (Reprinted from Kim S et al. *J Urol* 2011;186:1734–9. With permission.)

and treatment patterns. In Laos, bladder stones are a more frequent occurrence due to diarrhea and the early introduction of white rice, even in the neonatal period. Aboriginal children in Australia are predisposed to urate stones, often without underlying anatomic abnormalities. In such regions, chronic diarrhea can contribute to chronic metabolic acidosis, risking stone formation; one cause in young children is carbohydrate intolerance with enteric bacterial breakdown of sugars.[18] Regional variables may influence stone incidence. For example, in 2008 an outbreak of melamine-induced nephrolithiasis from contaminated infant formula occurred in China, affecting very young children. Melamine stones are thought to occur due to formation of a mesh network, which traps smaller acidic molecules in the urine and becomes trapped in renal tubules.[33]

EVOLVING TECHNIQUES

The management of upper urinary tract calculi has evolved dramatically in both adults and children in the last two decades. Smaller, more durable endoscopes and more effective lithotripsy technology have historically been adopted in adults prior to their acceptance in children. For both, minimally invasive techniques have revolutionized treatment and improved morbidity.

Since its introduction in the 1980s, extracorporeal shock wave lithotripsy (ESWL) transformed the management of pediatric upper tract calculus disease and remains very useful today. Other modalities of treatment, including ureteroscopy, percutaneous nephrolithotomy (PCNL), and combination treatment protocols, allow for flexibility in management. However, a consensus has not been reached as to the most effective and safe technique for upper tract urolithiasis, especially between ESWL and ureteroscopy. Despite the lack of compelling scientific data comparing these treatment methods in children, ureteroscopy has emerged in many centers as the first line of treatment. Given increased presentation of both simple and complex upper tract stones, the pediatric urologist must maintain a vast endourologic skill set and become familiar with constantly evolving minimally invasive technologies.

EVALUATION

Metabolic Workup

A metabolic stone evaluation is recommended for all pediatric first-time stone formers,[1] even in the context of underlying anatomic abnormality, such as ureteropelvic junction (UPJ) obstruction.[34] A complete metabolic blood profile and a 24-hour urine collection is obtained at least 1 month following stone treatment or upon stone diagnosis, depending on the urologist's preference. Unfortunately, there are no accepted standard reference ranges for 24-hour urine chemistries in the stone-forming pediatric population. Indeed, many pediatric urologists use adult standards to direct medical treatment because specific reference ranges are not readily available or require additional complicated calculations. Regrettably, there are significant differences between the normal ranges of urine chemistries in children and adults.[35,36] In addition, conflicting reports exist as to the commonality of metabolic disturbances in the presence of calcium-based stones.[13]

In the preliminary evaluation of pediatric stone disease, it is common to obtain 24-hour urine values for creatinine, sodium, calcium, oxalate, uric acid, and citrate. The very cumbersome nature of a 24-hour urine collection and the toilet training status of the child often limit accuracy and feasibility in the pediatric population. In light of this, random urine spot sample ratios have been used. Urine calcium–urine creatine ratios (Uca/Ucr), for example, have been used with sensitivities and specificities up to 90% and 84%, respectively, in the evaluation of hypercalciuria, a known risk factor for urolithiasis.[37] However, such a test is limited to one urinary metabolite and cannot be relied

on to monitor response to medical therapy. Furthermore, it is unreasonable to solely rely on urinary calcium excretion values as a proxy for overall metabolic disturbances.

It has been suggested that measurement of urinary supersaturation products (calcium oxalate and urate) may help to improve identifying those children at risk for stone formation. DeFoor et al. most recently determined that supersaturation levels of calcium oxalate, as well as calcium-to-creatinine levels, were significantly higher in children with stones than in controls.[38] However, this may have been reflective of differences found in urinary volumes. Lande et al. have demonstrated that low urine volumes in children often negate the benefit of pursuing urine supersaturation products in a stone workup.[39] Such conflicting data often confuse clinicians as to what urinary evaluation to pursue in the workup and management of pediatric stone disease.

Stone disease in the pediatric population has genetic, anatomic, metabolic, and dietary causes. There are numerous genetic causes of hypercalciuric nephrolithiasis alone that contribute to pediatric stone disease.[40] In this regard, the medical treatment always accompanies the endourologic management. *In order to fully treat the pediatric stone patient, there must be a focus on prevention through diet and medication monitoring. For this reason, the pediatric nephrologist is a critical player in the management and surveillance of these children*. Details regarding the metabolic workup and medical treatment of pediatric stone disease are beyond the scope of this chapter. Numerous pediatric nephrology resources are available. Alon provides an excellent pediatric nephrology review, including medication dosing by weight.[41] Litholink (www.litholink.com) is a commercially available 24-hour urine analysis, which stratifies risk profile for stone formation based on pH, volume, supersaturation profile, and concentration of lithogenic substances. However, 24-hour urine studies can be adequately performed through one's hospital with appropriate urologic or nephrologic counseling.

Imaging

Radiographic assessment of the child with calculus disease must be accurate, economic, and safe. *The goals of radiographic assessment include determination of stone location, size, density, and urinary tract anatomy*. Indications for assessment include acutely symptomatic children with a suspected calculus, or children with known calculus disease requiring follow-up evaluation to determine either stone burden or recurrence. Radiographic evaluation is also important in children with abnormal urinary tract anatomy that may predispose to calculus formation requiring eventual surgical management.

Radiographic imaging in children is unique in that a conscious effort is made to reduce the radiation burden during diagnostic workup. While older reports suggest that children present with classic renal colic only 50% of the time,[42] more recent reports suggest that abdominal and flank pain actually occur in the majority of children with stones. As no consensus exists on the optimal imaging regimen for a suspected urinary tract stone in a child, diagnostic imaging is typically the choice of the provider, with substantial provider variation.[4] *Initial screening with renal ultrasound or abdominal plain film alone, renal ultrasound plus abdominal film, or stone protocol CT is currently practiced*, with intravenous pyelography (IVP) having fallen out of favor. Brenner and colleagues penned a well-publicized 2007 review of the long-term radiation risks of CT in children in the *New England Journal of Medicine*, and since that time, the public has motivated clinical providers to reduce unnecessary CT exposure.[189] A contemporary large-scale retrospective review of more than 1 million pediatric emergency room records between 2003 and 2010 was the first to demonstrate a recent change toward decreasing CT utilization for commonly imaged areas of the body where alternative imaging, such as ultrasound, is available. Such was the authors' experience with reduced abdominal CTs for abdominal pain,[43] although this trend has not been specifically demonstrated for pediatric stone disease.

Unenhanced helical CT of the abdomen and pelvis to evaluate urinary tract calculi was first described in 1995 as the mainstay for calculus imaging in adolescents and adults.[44] Many, if not most, children with renal colic present to an emergency room, and *unenhanced helical CT is often performed as initial imaging for its efficiency and accuracy*. Typically, a thin-slice helical protocol is defined by narrow collimation ($\leq$5 mm). While calculi smaller than 5 mm can be missed between cuts, this is rare, with a reported sensitivity of 94%–99%.[45–48] In addition, CT also has the potential to rule out alternative diagnoses. *CT is also helpful in demonstrating secondary signs of acute obstruction, such as hydroureteronephrosis, renal enlargement, and perinephric or periureteric stranding; however, the latter findings may be less obvious or absent in pediatric patients due to comparably less retroperitoneal fat*.[49–51]

Passerotti et al. prospectively evaluated 50 children with both renal ultrasound and stone protocol CT scan, with blinded radiologic interpretation. Interestingly, although renal ultrasound was clearly less sensitive than CT at 76%, the majority of missed stones were 1–2 mm and within the kidney. The authors routinely recommend renal ultrasound, with the option of combined abdominal film and kidney, ureter, and bladder (KUB), as opposed to CT, as the first-line imaging modality. However, unenhanced stone protocol CT is recommended in cases where renal ultrasound quality is limited or diagnosis is uncertain, or for surgical planning of complex stone disease.[52] The cumulative effect of radiation exposure, the rising cost of healthcare, and the likelihood for stone recurrence in a young patient's lifetime must now be factored in, giving the pediatric urologist pause to consider how likely a CT is to change management decisions. Because children are at significant lifetime risk for recurrence of urolithiasis, the authors' reported 10 mGy unenhanced CT radiation dose can eventually multiply, potentially increasing the risk of future malignancy. Unfortunately, risk of radiation-induced malignancy is not a perfect mathematical model, and *there is no known threshold dose below which radiation exposure is safe*. The Biological Effects of Ionizing Radiation Panel VII (BEIR VII) report provides the existing data on the risks of ionizing radiation, based on available outcomes from Hiroshima and Nagasaki atomic

bomb survivors exposed to low-dose ionizing radiation of <100 mSv. Estimation of radiation-induced cancer risk is inherently flawed, however, given that no prospective, controlled epidemiologic studies exist to show adverse effects at radiation doses of <100 mSv.[53] Ultimately, close cooperation with our radiology colleagues can help to minimize radiation delivery to our pediatric patients when warranted.

Progress has been made in developing unenhanced CT protocols that minimize the radiation dosage while not compromising diagnostic information.[48,54,55] Experimental protocols utilizing anthropomorphic pediatric phantoms have been used in a number of studies to determine specific organ doses, calculate effective dose, and determine the lifetime attributable risk (LAR) for cancer incidence, and relative risk of cancer induction from a single scan under both standard- and low-dose modes.[56,57] Computer-simulated dose reduction has been useful in determining diagnostic thresholds in children with preserved accuracy of the CT scan.[58,59] *Perhaps most importantly, radiation exposure can also be reduced by limiting the number of CT examinations performed for weak clinical indications, scanning only the anatomic region of interest, and not performing both unenhanced and contrast-enhanced scanning unless absolutely necessary.*[60] For example, in a recent epidemiologic study by Routh and colleagues, 79% of children undergoing CT scanning as part of the workup for a stone episode had two or more studies performed. CT use was associated with older patient age, nonwhite race, and public insurance, but the treating hospital was the most important driver for CT use in children. Variability among hospitals for pediatric CT use was marked, ranging from 47% to 84%.[4]

Ultrasound is less accurate in the assessment of urolithiasis than CT, but it has the distinct advantage of no associated ionizing radiation. Therefore, ultrasound should be considered a screening tool in the workup of pediatric abdominal or flank pain. In the *acute setting*, when the child initially becomes symptomatic, ultrasound may miss migrating ureteral stones; however, it is very sensitive once hydronephrosis develops. The sensitivity of pediatric ultrasound for stone detection is 59%–78%, with up to 100% specificity.[47,52,61] Similar results have been reported in adults.[62,63] Many ultrasound proponents agree that ultrasound should be used in conjunction with KUB, given its added sensitivity for radiopaque stone detection. Symptomatic children with a known history of renal urolithiasis, or children on observation protocols, should typically be reevaluated with ultrasound and KUB to minimize cumulative radiation exposure.

Fluoroscopy has an important role in the real-time detection and management of urolithiasis in children, and the same important safety concerns exist with respect to radiation exposure as for CT. C-arm fluoroscopy is utilized in the surgical setting to assist in antegrade percutaneous access of the upper urinary tract and retrograde access of the lower urinary tract. Manipulation of endoscopic instruments in vivo often requires fluoroscopic monitoring. Fluoroscopy is also used during ESWL to assist in stone localization and monitor the effectiveness of treatment. Urologists must have a working understanding of the principles of fluoroscopy and be aware of the intraprocedure fluoroscopy time and energy settings to limit radiation exposure to both the pediatric patient and operative staff. Important variables, which will impact the dose of patient radiation when using fluoroscopy tables or C-arms, are the distance from the patient to the radiation source, gating down to the area of interest, pulsed instead of continuous dosing, and lead shielding of sensitive organs (gonads, thyroid, and breast tissue). In a recent prospective study from the Children's Hospital of Boston, dose rate settings were higher than recommended in 43% of cases and better C-arm positioning had the potential to reduce ionizing radiation exposure by 14%–49%.[64] Pediatric urologists should be cognizant of fluoroscopy time used and radiation source settings from the beginning of each case, especially since maintenance protocols and default settings are often not governed by the surgeon. Excellent reviews exist for the urologist and should be studied for both patient and personal safety when using fluoroscopy.[65,66]

CONSERVATIVE MANAGEMENT

Conservative management of pediatric nephrolithiasis is considered first-line treatment provided there is no evidence that an obstructing stone is harboring an infection or a child is failing to thrive as the result of his or her stone disease. Clinical scenarios, including fever, anorexia greater than 24 hours, persistent nausea and vomiting, and/or pain refractory to conservative measures, prompt endourological intervention. In the instance of a stone in a solitary kidney, early intervention over conservative treatment is favored. The same data are not available in children as in adults to determine the average time and likelihood of stone passage stratified by size. Small retrospective series suggest stones 4–6 mm or larger are likely to require endourologic treatment.[67,68] Interestingly, younger patients tend to present with renal stones, as opposed to older children, who present with ureteral stones,[13,42,47,69] often with larger stone burden. Larger, more proximal stone burden can negatively impact the likelihood for passage in young patients,[68] although studies of a similar stone burden using age 10 years as a cutoff failed to find a difference in spontaneous passage rates for younger versus older children.[69] The pediatric ureter is remarkably elastic for its small size, perhaps even more than the adult ureter.[70]

There have been many studies in adults evaluating the efficacy of medical expulsive therapy to facilitate distal stone passage. Use of alpha-antagonists, calcium channel blockers, and steroids has been shown to be effective. Based on the efficacy demonstrated in the adult population,[71] alpha-receptor antagonists, such as tamsulosin, may be offered on an individualized basis as adjunctive therapy to facilitate ureteral expulsion in children. A randomized prospective clinical trial recently completed in Egypt compared tamsulosin (0.4 mg for children 4 years and above, 0.2 mg if less than 4 years) to analgesic alone, finding enhanced stone-free rates of 87% versus 64% by 4 weeks for stones up to 1.2 cm.[72] Safety data concerning adult dose tamsulosin in children are only starting to become available, with this study demonstrating no increased rate of side effects.[72] Prior studies

of tamsulosin in pediatric nonneurogenic dysfunctional voiding also failed to demonstrate any adverse effect on blood pressure.[73] Some argue against the utility of medical expulsive therapy in children. For example, a Turkish study administering 0.03 mg/kg of the alpha-antagonist doxazosin versus analgesic alone did not demonstrate superior expulsive results with regard to distal ureteral stones up to 10 mm in children 2–14 years of age; this study was limited by the small number of overall patients who passed stones.[74] If a child fails a trial of spontaneous passage and definitive endourologic therapy cannot be accomplished immediately, a stent is placed and lithotripsy is delayed 2–4 weeks to allow for passive ureteral dilation, resolution of edema, and clearance of any infection, if present.

MANAGEMENT OF UPPER URINARY TRACT CALCULI

Pediatric Considerations

Special considerations in the endourologic management of stone disease in children include preservation of renal development and function, prevention of radiation exposure, and minimizing the need for retreatment. Despite advances in endourologic equipment and technique, controversy remains regarding the causality of diabetes or hypertension from ESWL, and whether ureteral orifice dilation during ureteroscopy leads to ureteral stricture formation or development of vesicoureteral reflux. International consensus is lacking as to the most effective surgical management of pediatric stone disease due to the lack of prospective randomized trials comparing treatment modalities and disparity in the access to emerging technologies.

Studies on stone fragment clearance suggest enhanced early stone fragment passage following ESWL for children with renal stones ranging from 1 to 2 cm in size (but not more than 2 cm), when compared with adult counterparts.[70] In contrast, Afshar et al. have demonstrated that residual stone fragments (RFs) of <5 mm in size are associated with adverse clinical outcomes in 69% of 26 affected renal units (stone growth, symptoms, or stone recurrence).[75] *Therefore, the surgeon's goal with pediatric urolithiasis is stone-free status*. Surgeon experience is paramount to facilitate complete stone clearance and minimize retreatment rates. The decision regarding the most efficacious primary treatment modality must be individualized per child based on age, anatomy, location, and composition of stone burden.

Antibiotic Use

In line with the 2008 American Urologic Association best-practice statement on antibiotic prophylaxis, ≤24 hours of perioperative antibiotics is indicated in all patients undergoing upper tract instrumentation.[76] In children, appropriate agents include trimethoprim-sulfamethoxazole, first- and second-generation cephalosporins, and ampicillin in combination with an aminoglycoside. A urine culture is mandatory before all upper tract procedures to determine if the urine is sterile, and culture results are used to guide preoperative antibiotic therapy, particularly for percutaneous procedures, patients with high-grade obstruction, or patients with an indwelling stent.[77] In our practice, children with a negative urine culture undergoing uncomplicated ureteroscopy (URS) procedures receive perioperative cefazolin, and all children undergoing a percutaneous procedure or who have a preexisting ureteral stent or nephrostomy tube receive a fluoroquinolone or ampicillin or gentamicin. Use of postoperative antibiotics is controversial and is determined on an individual child basis, especially with recent data demonstrating an increased risk of developing resistant bacterial strains with prolonged use of prophylactic antibiotic therapy.[78] Fluoroquinolones are often safely used in children, but the side effect profile can be serious due to the proposed destructive effect on collagen and connective tissue fibers in weight-bearing joints.[79] Cartilage abnormalities have been identified in juvenile animals after quinolone use, as well as increased rates of arthralgia in children compared with controls 1 year following quinolone administration (3.4% vs. 1.8%, respectively).[80] Currently, fluoroquinolones are routinely used for pediatric indications of *Pseudomonas aeruginosa* infections, beta-lactam and macrolide-resistant otitis media, resistant gram-negative infections, and bacterial meningitis.[81] Fluoroquinolones are not contraindicated in children, but parents should be counseled on theoretical cartilage damage and arthralgia if electing their use.

SHOCK WAVE LITHOTRIPSY

The emergence of shock wave lithotripsy (SWL) revolutionized the minimally invasive treatment of adult urolithiasis during the early 1980s. Since the initial report of successful SWL use in children in 1986,[82] large series have reported complication, safety, and stone-free rates comparable to those of adult cohorts[15,83–89] (Table 27.1). When used as a primary treatment option for upper tract calculi, SWL efficacy ranges from 68% to 84%.[15,35,83] SWL has been a preferred treatment modality for uncomplicated renal and proximal calculi of ≤15 mm in the pediatric population. In a contemporary series of 216 children (mean age 6.6 years) with a mean stone size of 14.9 mm undergoing SWL with the Dornier HM3 lithotriptor, Landau et al. reported a 3-month stone-free rate of 80%, demonstrating that efficacious stone-free rates can be achieved in appropriate candidates.[94] *Although retreatment rates are high, complications are typically low, with severity ranging from hematuria and ecchymosis to obstruction with sepsis*.[95]

Although well tolerated in children, current stone-free rates with SWL are difficult to interpret from the existing body of data due to discrepancies between studies with regard to type of lithotriptor, number of shocks administered, and retreatment rates. *Recent data suggest that stone-free rates in children with a history of urologic condition or urinary tract reconstruction are quite low (12.5%) and with alternative surgical techniques available, these children may be better served with URS or PCNL*.[91] Despite encouraging results, SWL has not been

TABLE 27.1 Outcomes with large series of shock wave lithotripsy in children

Report	Children/ renal units	Lithotriptor	Mean age (years)	Stone location (%)	Mean size (mm)	Retreatment rate (%)	Stone-free (%)	Complications (%)
Habib et al.[90]	150/186	Dornier DoLi S; Dornier S EMSE 220F-XXP	6.6	90.3 R 9.7 U	13	49.5	89.2	Overall—18.7 Colic—10.7 Steinstrasse—6.7 Fever—1.3
Nelson et al.[91]	101/114	Dornier Compact Delta	10.5	87.4 R 12.6 U	8	22	58.6	Overall—7 Ureteral obstruction—2 Fever—3 Urethral stone—0.7 Hematoma—0.7 Hospital admission—3.4
Muslumanoglu et al.[92]	192/192	Siemens Lithostar Plus	7.3	39 PU 19 MU 134 DU	n/a	45.1 PU 62.5 MU 49.6 DU	94 94 89	UTI—1 Colic—2.3
Demirkesen et al.[89]	126/151	Siemens Lithostar	8 (median)	66.9 R 33.1 LP	10 R 6 LP	40	71.5	Overall—7.2 Fever—0.8 Steinstrasse—6.4
Raza et al.[93]	122/140	Piezolith 2300; Dornier Compact Delta	7.7	n/a	17.9	n/a	69	Fever—2.9 Colic—7.2 Steinstrasse—2.4
Aksoy et al.[87]	129/134	Dornier MPL 9000	8.7	84.4 R 15.6 U	15.7	n/a	85	Overall—14.7 Steinstrasse—5.4 UTI—7.8 Hematoma—0.8
Muslumanoglu et al.[85]	344	Siemans Lithostar Plus	8.7	57.1 R 42.9 U	n/a	53.9	73.3	Overall—9.6 Steinstrasse—7.8 UTI—1.2 Colic—2.9
Rizvi et al.[15]	262	EDAP LT02 Technomed	n/a	67.6 R 32.4 U	n/a	29.5	84.2 R 54.1 U	Colic—10.1 Fever—8.5 Steinstrasse—1.1 Hematuria—11.3
Ather and Noor[86]	105	Dornier MPL 9000	5.6	100 R	15	n/a	95	Colic—2.9 Steinstrasse—1.9 UTI—2.9
Elsobky et al.[84]	148	Dornier MFL 5000 (106); Echolith MedTech (42)	11.2	92.6 R 7.4 U	10.2	64	86	Steinstrasse—0.7
Myers et al.[83]	446	Siemans Lithostar	13.7 R 14.1 U	53.4 R 46.6 U	12.3 R 7.3 U	10.7 R 3.5 U	67.9 R 91.1 U	Sepsis—0.2

Abbreviations: R, renal; U, ureteral; LP, lower pole; UTI, urinary tract infection; PU, proximal ureter; MU, mid ureter; DU, distal ureter; n/a, not applicable or data not available.

approved by the Food and Drug Administration for use in children, although it is a widely accepted treatment modality.

SWL Technique in Children

General anesthesia is administered in a majority of smaller children to avoid both patient and stone motion, and the need for repeated repositioning. With modern lithotriptors, intravenous sedation has been successfully employed in select older children.[96] Bowel preparation is seldom utilized to avoid dehydration and electrolyte imbalance postoperatively. The number of shocks delivered and the kilovoltage used vary per lithotriptor, but the current consensus is that low-power settings (17–22 kV) be used to prevent stone migration during the procedure, with 3000 shock waves per session (<2000 in very young children).[95] A recent report assessed and compared the

number and intensity of shock waves required for stone fragmentation in 44 children (mean age 5.9 years) and 562 adults (mean age 40.9 years). With an equivalent number of sessions (1.1 vs. 1.1), the mean number of shock waves (950 vs. 1262, $p < 0.001$) and the kilovolts required (11.8 vs. 12.4, $p < 0.001$) were significantly reduced in the pediatric cohort.[97]

Whether or not to place a ureteral stent prior to ESWL in children remains a controversy and a matter of personal preference. A meta-analysis of eight adult SWL trials suggests ureteral stenting may reduce the rate of Steinstrasse, although overall stone-free rates were not improved and lower urinary tract symptoms were worse.[98] Data are inconclusive in children, but the pediatric ureter is believed to better expel stone fragments after SWL, and in children, well-tolerated Steinstrasse fragments may be conservatively managed. Although prestenting rates are not consistent across series, *current relative indications include cases of solitary kidneys, staghorn calculi, large ureteral calculi, obstruction, or abnormal anatomy and are not based on total stone burden*. Ureteral catheters that can be used for retrograde opacification are occasionally placed immediately prior to SWL to aid in the localization of radiolucent calculi.

Stone Size, Location, Composition, and Patient Age

While early series focused primarily on the feasibility, safety, and efficacy of SWL in children, recent efforts have centered on identifying demographic, anatomic, and stone-related prognostic factors for treatment success. Onal and colleagues have recently constructed a nomogram based on Turkish children to assist pediatric urologists in predicting stone clearance following SWL, although this has not been externally validated. Multivariate analysis revealed younger age, female gender, lower stone burden, and lack of prior ipsilateral stone treatment to be positively associated with stone clearance.[99] SWL is currently considered the primary treatment modality of choice for upper tract calculi of ≤15 mm in children,[95] but evidence supporting this stone size cutoff is lacking. Ather and Noor, for example, analyzed the correlation between stone size and clearance in 105 children younger than 14 years of age. They reported an overall stone-free rate of 95% after a mean of 1.7 SWL treatments; 5% of patients required additional procedures as adjuncts to SWL. In this cohort, the mean stone size in the treatment success group was 14 mm, compared with 16 mm in the treatment failure group.[86] In a larger series of 150 children, Habib and colleagues recently found that larger stone size was significantly associated with SWL failure and retreatment; stones of >3 cm failed 66.7% of the time, and stones of >1.35 cm accounted for 80% of the failures.[90] In contrast, Elsobky et al. reported a 91% stone-free rate versus 75% stone-free rate for mean stone diameters of less than and greater than 10 mm, respectively.[84] Recently, Shouman et al. reported on a series of 24 children with a mean stone size of 31 mm undergoing SWL with the Dornier DoLi S device. In 53 sessions requiring a mean number of 3489 shock waves per session, stone-free and complication rates were 83.3% and 25%, respectively.[100] *While it is possible to treat very large stone burdens with SWL, concerns include the necessity of more shock treatments, more frequent retreatment sessions, and an increased risk of postoperative obstruction*. Further study delineating a clear size cutoff for uncomplicated upper tract stone burden is required to effectively counsel parents regarding the most effective first-line therapy for renal calculi between 1 and 1.5 cm.

Renal anatomy and stone location has been the subject of recent interest. Badawy and colleagues have suggested that prior urologic surgery and ureteral stones of >1 cm are associated with lower SWL success rates, potentially benefitting from other forms of surgical management.[101] Previously operated urinary tracts (for UPJ obstruction and ureterovesical junction [UVJ] surgery) were found in 16 of the 19 (84%) renal stones failing SWL in this series, which is echoed in other reports.[91] The subject of frequent debate in the adult population, the most effective management of lower-pole calculi in children has yet to be determined. Stone-free rates from initial small retrospective SWL series range from 56% to 61%,[102,103] with retreatment rates as high as 40%.[103] *SWL failure and the need for retreatment were associated with increased mean stone burden,*[103] *increased infundibular length,*[102] *and an infundibulopelvic angle of greater than 45°.*[102]

Staghorn calculi are uncommon in children and represent a management challenge. Although monotherapy success rates are low in adults, acceptable stone-free rates in children have been achieved with SWL. In 23 children stratified by age with a mean stone burden of 1.6 cm, Lottmann et al. reported an overall stone-free rate of 82.6%, with only one case of symptomatic obstruction. A ureteral stent was placed in 22% of children, and these authors reported an 88% stone-free rate in children less than 2 years of age compared with 71% in children aged 6–11 years.[104] In 42 children with a mean stone burden of 3.2 cm stratified by ureteral stent placement, Al-Busaidy et al. reported an overall stone-free rate of 79%. While stent placement did not affect stone-free rates, they found that stent placement significantly reduced the major complication rate.[105] *The superior success rates with SWL monotherapy in children compared with adults have been attributed to softer stone composition, smaller relative stone volume, increased ureteral compliance to accommodate stone fragments, and smaller body volume to facilitate shock transmission.*

SWL safety and efficacy have been demonstrated even in very young children. McLorie et al. treated 34 children younger than 3.5 years old (mean age 23 months) and reported an 86% overall stone-free rate (66% after one treatment) without major complications.[106] Some authors suggest that proximal ureteral stones have success rates similar to those for renal stones in pediatric series,[83,91,107] although others report reduced treatment success for all levels of ureteral stones.[101] Treatment of mid- to distal ureteral calculi had been historically avoided in children due to difficulties with localization over the sacroiliac joint and concern regarding possible injury to developing reproductive systems. The greater and lesser sciatic foramina have been utilized as a blast path to treat distal stones in children with success rates of 77% and 100% at 2 weeks and 3 months, respectively, in 22 children, with a mean distal stone burden of 6.8 mm.[108]

SWL success by stone composition is similar between the adult and pediatric populations. Cystine stones are uniquely challenging due to their durability and high recurrence rates; however, calcium oxalate monohydrate, brushite, and matrix stones also have less favorable response rates to SWL.[109] While SWL monotherapy has demonstrated variable results in adults, there are few reports in the pediatric population. In a small recent series, Slavkovic et al. reported a 50% stone-free rate in six children with cystine stone burden ranging from 2 to 2.5 cm. Although stone-free rates were low, fragmentation was achieved in 100% of patients and the stone dissolution was achieved with medical therapy in the remaining children following SWL.[110] Cystine stones formed within 2 years of therapy may be more easily fragmented with SWL, and stone number, rather than diameter, may better predict success.[95]

Additional factors to optimize the success of stone clearance with SWL include reducing the shock wave rate, improving acoustic coupling, power ramping (gradual increases in kilovolts), and utilizing dual-energy CT for stone composition.[109,111,112] Lingeman et al.[112] reported on several methods currently under investigation to improve the efficiency of SWL, including improvements in lithotriptor technology and lithotripsy technique. The former includes acoustic tracking for stone targeting, feedback to ensure adequate acoustic coupling, assessment of stone breakage, transcutaneous focused ultrasound to help clear RFs, and employing wider focal zones. *Regarding technique, it seems that minimizing both the total shock wave dose and rate is prudent to limit renal injury, especially in children*. To enhance efficacy, the pediatric urologist should optimize acoustic coupling by eliminating air pockets between the patient and treatment head, which can reflect 99% of shock waves. Historically, a water bath was used for the Dornier HM3, and a partial water bath is still used for the Storz SLX (Storz Medical, Tägerwilen, Switzerland); gel is the most common interface of other devices.[112]

Limitations and Concerns

In children, there is currently no consensus regarding the maximum size of RFs that are considered clinically significant,[77,95] and as a result, there is no clear definition as to what constitutes "stone-free" status. While children have been shown to have a greater capacity to clear fragments than adults,[70] the presence of RFs has been correlated with adverse clinical outcome.[75] Afshar et al. followed 26 renal units with RFs of $\leq$5 mm and reported that while 31% were asymptomatic with no fragment growth, 69% had adverse clinical outcomes, including RF growth or clinical symptoms. Patients with RFs had a significant increase in adverse clinical outcome compared with stone-free subjects, and the presence of metabolic disorders was associated with RF growth.[75] For these reasons, metabolic evaluations are now routinely being performed in children with a history of calculi, and every attempt should be made to achieve stone-free status.

Although SWL is well tolerated in children with few complications, stone-free rates following single-session monotherapy can remain as low as 44%.[85] As a result, children are subjected to multiple treatments requiring general anesthesia.[96] *The need for multiple treatment sessions is concerning since the long-term effects of shock waves on renal tissue are unclear*. In adults, shock waves may result in renal vasoconstriction with renal tubular injury and subcapsular hematoma from cavitation and shear forces, which are dependent on the kilovoltage applied.[113] In 2006, a large retrospective series of 340 adult patients with a mean follow-up of 19 years post-SWL raised initial concern regarding increased risk of hypertension and diabetes mellitus due to incidental shocks to the pancreas.[114] However, since that time investigators from the same group at the Mayo Clinic reevaluated both questions of increased diabetes and hypertension risk with a population-based cohort study via the Rochester Epidemiology Project. This more recent study found no association between SWL and subsequent development of either disease.[115] Janetschek et al. found that development of hypertension in their retrospective series was highly correlated with disturbances in renal perfusion, as measured by elevated resistive indices, and this risk was purely age dependent, essentially confined to patients over 60 years old.[116] Additionally, rat and rabbit ovaries have been evaluated following shock wave therapy, finding no histopathologic, apoptotic, or reproductive impairment.[117,118] Animal testes exposed to shock waves do appear to undergo early histologic changes with vascular congestion and focal hemorrhage; however, these changes appeared reversible with time and did not impact function as assessed by hormone levels and fertility.[119] Adult male rabbits exposed to 2000 shock waves were found to have vacuolization of Sertoli cells, but no changes in sperm morphology up to 1 week postintervention.[120] Long-term disease evaluation following SWL is extremely limited in children, but thus far adult studies do not associate SWL with long-term renal, gonadal, or pancreatic impairment.

Existing data have failed to demonstrate significant renal scarring or functional impairment in pediatric kidneys post-SWL. Retrospective evaluation of 14 children following SWL and PCNL did not find renal morphologic or functional impairment when measuring glomerular filtration rate (GFR) and serial radionuclide (dimercaptosuccinic acid [DMSA]) scans at 3 and 6 months postintervention. While three children had preexisting renal scars, importantly, no new renal scars occurred.[121] A larger Spanish study of 18 children undergoing exclusively SWL demonstrated a majority of children did not experience long-term renal scarring, as measured by radionuclide scintigraphy (DMSA); 1 child had impaired ipsilateral renal growth and reduced tubular function after a three-staged procedure.[122] Recent prospective, controlled evaluation by Fayad and colleagues compared renal growth with renal ultrasound–measured bipolar length during the first year after SWL. No difference was found between children undergoing SWL and those who had no renal procedure at both 6 months and 1 year follow-up; further analysis revealed that neither age, number of SWL sessions, or number of stones altered that outcome.[123] In addition, Sarica et al. followed 35 children with blood pressure checks every 6 months, finding no adverse impact on pediatric hypertension or renal parenchyma as measured by renal ultrasound.[124] Finally, an animal model,

which utilized immature, 7-week-old rabbits undergoing SWL, failed to demonstrate renal growth impairment, although mean arterial pressure and histologic changes were found in adulthood.[125]

URETEROSCOPIC MANAGEMENT OF UPPER URINARY TRACT CALCULI

The indications for primary ureteroscopic management of upper tract calculi in children have significantly expanded. Increasingly smaller versions of endourologic instrumentation and the holmium:YAG laser make treatment of calculus disease throughout the entire pediatric urinary tract safe and effective in the acute setting. Adoption of ureteroscopy in the treatment of pediatric upper tract calculus disease lagged behind the adult experience because of concerns regarding large ureteroscope caliber causing greater complications in children. However, evolving experience with pediatric ureteroscopy and recent large retrospective series have reported enhanced stone-free rates and similarly low complication rates when compared with SWL, validating it as a staple in children.

Indications

Since the mid-1980s, with the acceptance of SWL as the primary therapy for upper tract calculi of <1.5 cm, ureteroscopy has been historically utilized for calculi below the iliac crests, and for upper tract calculi after SWL failure.[77] Ureteroscopy was not considered primary therapy for upper tract stones in children due to complications from ureteral ischemia, perforation, stricture formation, and development of vesicoureteral reflux as a result of dilation of small-caliber ureteral orifices.

With significant improvements in both the miniaturization and durability of endoscopic equipment and the acceptance of the holmium laser, ureteroscopy has become a more attractive option in young children. Early series using rigid ureteroscopy for distal stones reported stone-free rates ranging from 86% to 100% with minimal complications (Table 27.3).[15,67,126–131] Children randomized to either ureteroscopy or SWL as primary therapy for distal ureteral stones were reported to have a significantly higher stone-free rate after one treatment (94% vs. 43%) for those treated with ureteroscopy.[128] Another group reported experience using 4.5, 6, and 8 Fr rigid ureteroscopy in treating proximal ureteral stones, with a mean age of 10.7 years. Ureteral dilation was not performed in any of the cases, and 100% of children were rendered stone-free.[132] *The results of these retrospective studies have begun to refute the notion that dilation of the pediatric ureter will result in vesicoureteral reflux or the development of ureteral strictures.* In a systematic review of the literature encompassing 221 pediatric ureteroscopies, Schuster et al. noted only two ureteral strictures and a low incidence of vesicoureteral reflux.[127] Newer 4.5 Fr semirigid ureteroscopes, with working ports that accommodate 2.4 Fr endosurgical instrumentation, extend the versatility of managing distal ureteral calculi in most pediatric patients without predilation.

Standardization in the treatment of distal calculi in children has led a number of centers to expand ureteroscopy to the treatment of upper tract calculi (Table 27.2). Comparable stone-free rates approaching 100%, with complication rates similar to those of the adult population, have recently been reported.[130,132,136–138] Smaldone et al. reported a 91% stone-free rate with a mean follow-up of 10 months in a series of 100 children with a mean stone diameter of 8.3 mm, 52% of which had upper tract calculi. Nine percent of these children underwent staged procedures. They reported a 4.2% perforation rate managed with ureteral stenting and one distal ureteral stricture requiring open neocystostomy.[136] Corcoran et al. reviewed a cohort of 47 children (mean age 9.4 years) with upper tract calculi managed with flexible ureteroscopy and holmium laser lithotripsy. An 88% stone-free rate with a mean stone burden of 10.2 mm was reported, with 26% requiring staged procedures.[138] *These authors concluded that because of improved ureteroscopic access to the pediatric upper tract, calculi up to 15 mm were safely and as effectively treated in children as adults.* Even with outstanding pediatric ureteroscopic technology, pediatric ureters may require a period of stenting prior to embarking on endoscopic treatment. For example, a smaller-caliber ureter, resistant to instrumentation, may be passively dilated with an indwelling stent over 2–8 weeks (Figure 27.3).

Adoption of techniques utilized in the adult population, most notably sequential coaxial and balloon dilation of the ureteral orifice and use of ureteral access sheaths, has further facilitated access to the pediatric urinary tract. Initially described in eight children by Singh et al.,[139] ureteral access sheaths have been shown to facilitate repetitive upper tract access, reduce intrarenal pressures, decrease operative time, and improve stone-free rates in adults. Access for the treatment of lower-pole calculi is possible with the use of ureteral access sheaths and a 6.9 Fr flexible ureteroscope, a stone location that would have previously required SWL or PCNL. Cannon et al. reported a 76% stone-free rate in 21 children with lower-pole calculi and a mean stone diameter of 12.2 mm. After a mean of 11.4 months, no major complications were observed.[137] *Therefore, many centers are transitioning from SWL to ureteroscopy for both safety and lower retreatment rates. Current relative contraindications to ureteroscopic management include staghorn stones in recurrent stone formers, anatomic anomalies making retrograde access difficult, and previous endoscopic failure.*

Equipment

Having an updated and well-stocked system that is familiar to the operative staff is vital to efficient management. It usually falls on the nursing staff to care for the delicate instruments and keep up on repairs so that the instruments are operational when needed; maintenance is often needed after 20–30 uses. A "basic" ureteroscopic kit is listed below; however, variation exists based on manufacturers. Various arrays of semirigid and flexible pediatric ureteroscopes, in addition to ureteral access sheaths, are available from numerous companies.[140] In general, semirigid ureteroscopes usually have a 2.4–3.5 Fr working port (Figure 27.4), and flexible ureteroscopes a 1.8–3.5

TABLE 27.2 Outcomes for series treating pediatric stones with ureteroscopy

Study	No. Children/ no. procedures	Mean age (years)	Stone size (mm)	Stone location (%)	Ureteral orifice dilation (%)	Stone-Free (%)	Staged (%)	Postoperative stenting (%)	Complications (%)
Rigid ureteroscopy for mid- to distal ureteral calculi									
Galal et al.[133]	18/18	7.6	7	100 U	44	89	n/a	75	Hematuria—13 Fever/renal colic—19
Gamal et al.[134]	21/21	8.5	6.5	100 U	0	95.2	5	0	0
Raza et al.[88]	35/52	5.9	9.4	100 U	3.9	79.3	28.6	n/a	Ureteral stricture—2 Fever—10 Ureteral perforation—6
Al-Busaidy et al.[105]	43/47	6.2	12.6	100 U	n/a	93	n/a	n/a	Ureteral perforation—4 Ureteral stricture—2 Fever/VUR—12
Bassiri et al.[135]	66/66	9	8	100 U	37.9	88	n/a	n/a	Renal colic—1.5 Gross hematuria—16.7 Pyelonephritis—4.5
Rigid and flexible ureteroscopy for upper tract and renal calculi									
Unsal et al.[191]	16/17	4.2	11.5	100 R	29.4	88	6	100	Ureteral extravasation (UVJ)—6
Smaldone et al.[136]	100/115	13.2	8.3	52 R 48 U	70	91	9	75	Ureteral perforation—4.2 Ureteral stricture—1
Cannon et al.[137]	21/21	15.1	12.2	100 LP	81	76	14	71	0
Corcoran et al.[138]	47/61	9.4	10.2	100 R	91	88	26	70	Ureteral perforation—9
Minevich et al.[130]	58/65	7.5	n/a	64.6 U 35.4 P	30	98	n/a	85	Ureteral stricture—1.3

Abbreviations: EHL, electrohydraulic lithotripsy; R, renal; U, ureteral; LP, lower pole.

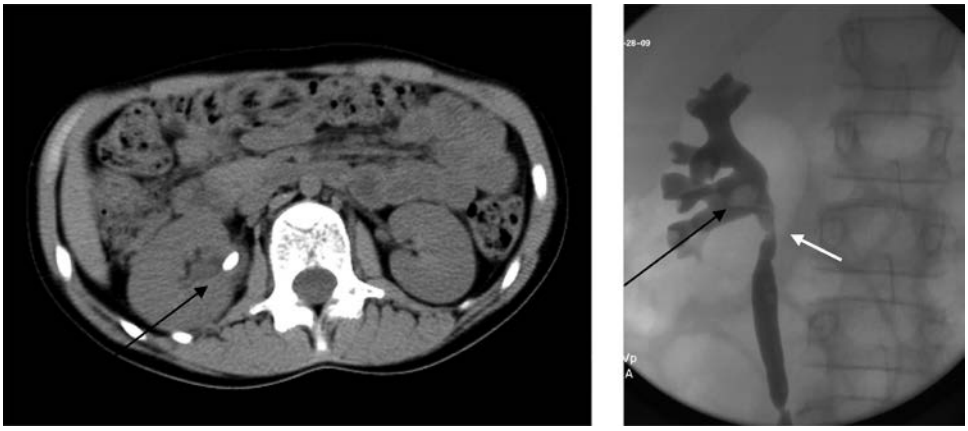

FIGURE 27.3 CT scan and retrograde pyelogram in a 10-year-old female with glucose transport deficiency demonstrating a 9 mm renal pelvic stone (black arrows). A metabolic defect was identified: hypocitraturic hypercalciuria. Primary ureteroscopy could not be accomplished due to a narrowed segment of the proximal ureter (white arrow) from stone-induced edema, but was successful after 8 weeks of ureteral accommodation with an indwelling stent.

Fr working port (Figure 27.5). With flexible ureteroscopes, deflection of the distal tip up to 270° can facilitate access to most lower-pole stones. Deflection can be limited with instruments placed in the working channel; therefore, use of smaller baskets (1.9 Fr nitinol) and laser fibers (200 μm) will improve lower-pole renal access.

Ureteroscopes
- 6.9 Fr flexible ureteroscope
- 4.5 and 6.5 Fr semirigid ureteroscopes

Endourologic equipment
- Guidewire array: 0.035 sensor, 0.018–0.025 straight or angled glidewire

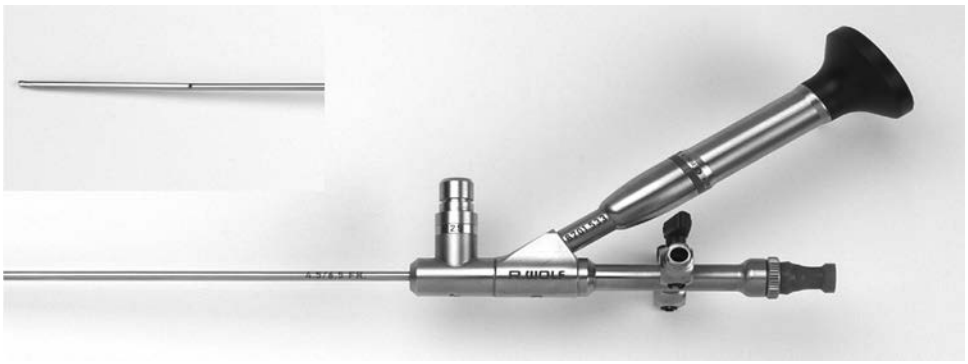

FIGURE 27.4 Pediatric semirigid self-dilating ureteroscopes may be used for rigid ureteroscopy in toddlers. A 4.5 F distal beak (inset) allows easier passage to facilitate dilation with the 6.5 F proximal component. (Picture provided by Richard Wolf. Copyright © 2012, all rights reserved.)

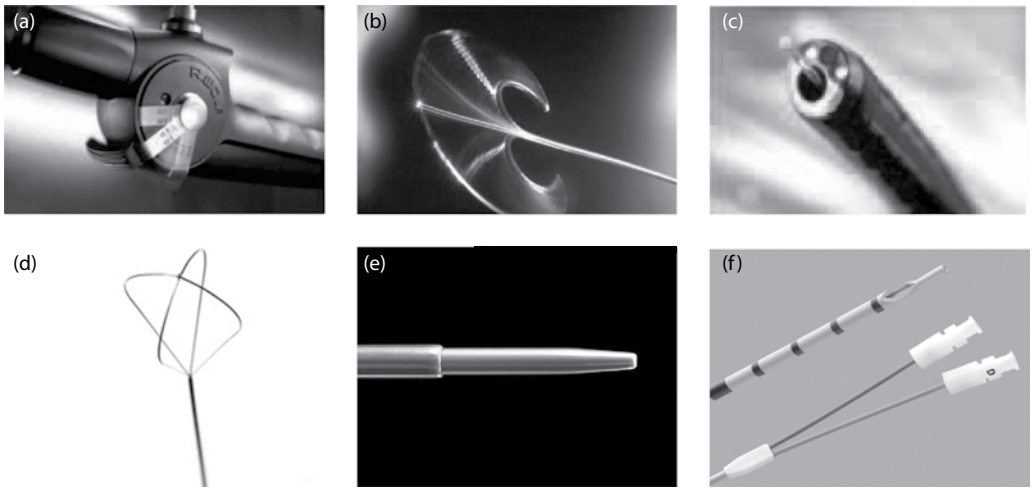

FIGURE 27.5 (a and b) Flexible ureteroscopes are capable of thumb-controlled, biplanar 270° deflection. (c) Working channels from 1.8 to 3.6 Fr can accommodate working elements, such as a Ho:YAG laser fiber. (d) Nitinol zero-tip baskets ranging from 1.9 to 3.2 Fr impair deflection of flexible ureteroscopes the least, with minimal risk of mucosal injury. (e) Coaxial 8 Fr inner/10 Fr outer dilator set (tip shown) passively dilates, and also calibrates, the ureter to facilitate ureteroscopic sheath placement. (f) A dual-lumen catheter allows safe passage of two wires (working and safety wires) into the renal pelvis with passive ureteral dilation to 10 Fr. (Picture provided by Richard Wolf. Copyright © 2012, all rights reserved.) ([d] From Honey JR. *J Endourol* 1998;12(6):529–31; Lukasewycz S et al. *J Urol* 2004;172(2):562–4.)

Basket devices: Zero tip
8/10 Fr coaxial ureteral dilators
Ureteral access sheaths (9.5, 11, and 12 Fr internal diameter)
Double-J ureteral stent array: 3, 4.8, and 6 Fr
Ho:YAG Laser fiber and source (200 μm fiber for best irrigant flow and deflection)

Ureteroscopic Technique in Children

All ureteroscopic procedures are performed under general anesthesia with paralysis to prevent patient movement and minimize the risk of ureteral perforation. Occasionally, expeditious stone extractions for predilated patients or distal ureteral stones require deep anesthesia but not paralysis. Close communication with anesthesia regarding the expected duration of the procedure is essential. When clinically appropriate, a urine culture should be confirmed prior to surgery. First- or second-generation cephalosporin antibiotic prophylaxis is administered within 30 minutes of procedure start, although an oral fluoroquinolone or sulfamethoxazole-trimethoprim is acceptable. Patients are placed in the lithotomy position, and rigid cystoscopy is performed with a 7.5, 11, or 18 Fr cystoscope for infant, school, or adolescent ages. This allows the surgeon to inspect the bladder for stone passage and anatomic variant, and to perform a retrograde pyelogram. A safety wire (typically 0.035 sensor) is placed under fluoroscopic guidance. Wires of 0.018- to 0.038-inch diameters exist, with either polytetrafluoroethylene (PTFE) or nitinol coating. Nitinol is a nickel-titanium alloy exhibiting excellent shape memory and elasticity at body temperatures, making it safe in the delicate pediatric ureter. Nitinol's hydrophilic properties are what allow the tip of sensor wires or glidewires to access tortuous ureters. Glidewires have so much "slip" that they require handling with a moist sponge to prevent loss of the wire and are not recommended as safety wires for this reason; safety wires typically have an inner

stainless steel core for stability and outer PTFE coating to reduce friction of instrument passage. Infants typically require passive dilation over a number of weeks with a 3.7 Fr ureteral stent, placed using the supplied 0.018 guidewire, prior to any ureteral manipulation. Initial ureteral orifice dilation is performed under C-arm fluoroscopic guidance with a 8 Fr inner/10 Fr outer diameter (8/10 Fr) coaxial dilator, ureteral dilator set (6–14 Fr), or 10 Fr dual-lumen catheter if the patient has not had a period of prestenting. Balloon dilation of the orifice is reported but remains controversial, due to anecdotal cases of ureteral strictures or de novo vesicoureteral reflux, and is based on surgeon preference.[130] It is the authors' preference to avoid balloon dilation anywhere along the ureter, and if encountering difficulty with passage of an 8/10 Fr coaxial dilator, our preference is then to place a stent and return for ureteroscopic completion. In our practice, as has been established by others, stent length (cm) is typically determined by "Age + 10" until adolescence, at which point cross-sectional imaging (if available) is helpful in measuring radiographic length from the renal pelvis to the bladder trigone. Data on stent tolerance in children are extremely limited. Although Hubert and Palmer reported no bladder spasms in their retrospective cohort of 26 children (age 14 or less),[141] Wang and colleagues indicate that 32% of their 96 children had stent-related symptoms sufficient enough to call the surgeon's office after ureteroscopic treatment.[142] In the authors' experience, stent-related symptoms worsen with increasing age, most notably in adolescence.

The decision to use a flexible (6.9 Fr) or semirigid (7.5 Fr) ureteroscope is made based on size and location of the stone, anatomic factors, and individual surgeon preference. Rigid or semirigid ureteroscopy for ureteral calculi is routinely performed with a safety wire in place, while flexible ureteroscopy is performed with both a safety and a working wire in place. Ureteral access sheaths (internal diameter of 9.5, 11, or 12 Fr; outer diameter of 11, 13, or 14 Fr) are routinely utilized to facilitate flexible ureteroscopy, especially in cases of large proximal ureteral stones and heavy renal pelvis stone burdens. *Access sheaths may also serve to facilitate flexible ureteroscopy when altered anatomy or tortuous ureters are encountered* (Figure 27.6). Advances in flexible ureteroscope have resulted in improved image quality to ensure better stone clearance, especially with the transition from fiber-optic to digital imaging in 2007 with the Gyrus ACMI®. Since that time, Olympus has produced the URF-V and Storz the Flex-X. The Storz Flex-X flexible ureteroscope has a maximum diameter of 8.5 Fr, is the smallest flexible ureteroscope available at this time, and passes easily through the smallest ureteral access sheath (9.5/11 Fr). This makes flexible ureteroscopy through even infant ureters feasible (Figure 27.7).

Irrigating fluid, which may be used under pressure, should be isotonic and kept at body temperature to avoid hyponatremia and hypothermia. Flow will be limited through the 11 Fr access sheath. Calculi are basket extracted when feasible or fragmented using the holmium:YAG laser to facilitate removal. *The decision to place a ureteral stent postoperatively is made based on the duration of the procedure, number of passes with the ureteroscope, and degree of visible ureteral trauma or edema at the conclusion of the procedure.* If the child can tolerate leaving a urethral string in place for 3 days to 1 week, the patient's parents are asked to remove the stent at home. If left in place for greater than 1–2 weeks, the dangle is removed from the stent (due to theoretical risk of pyelonephritis and possible stent dislodgement) and the stent is subsequently removed with a brief anesthetic.

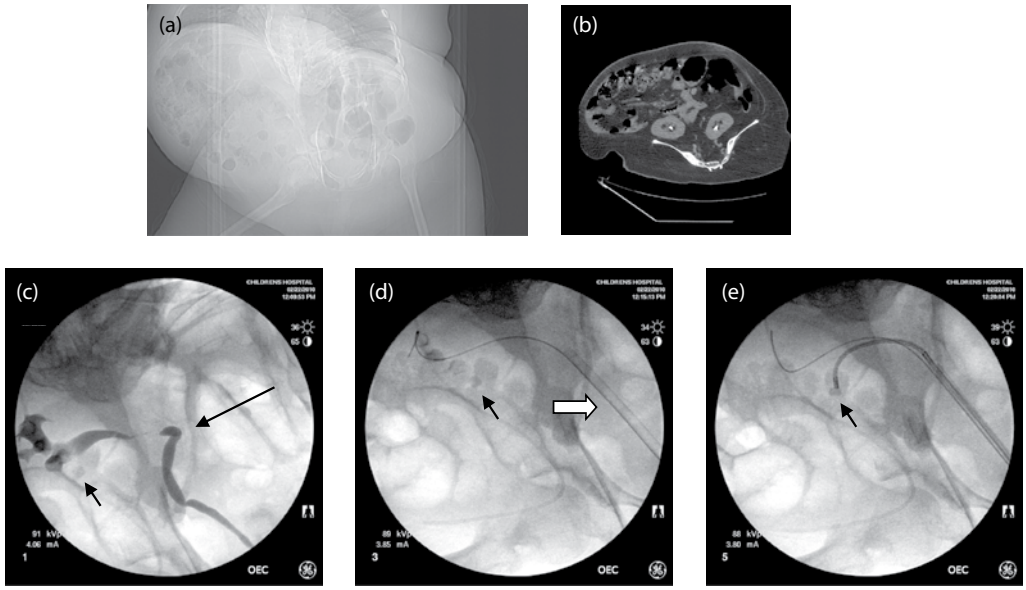

FIGURE 27.6 Altered anatomy in a 17-year-old male spina bifida patient who underwent a high thoracic myelomeningocele closure at birth (a). A CT scan performed for a gross hematuria workup revealed bilateral nephrolithiasis in pelvic kidneys (b). The right retrograde pyelogram (c) demonstrated the lower pole stone (short arrows) and a tortuous ureter almost taking a perpendicular course (long arrow). Placement of a ureteral access sheath (d) straightened the ureter (white arrow), allowing easier access to address the stone with a flexible ureteroscope (e).

FIGURE 27.7 One-year-old female successfully managed with flexible ureteroscopy for a 1.5 cm stone with prestenting, given the large stone burden. A 9.5/11 Fr ureteral access sheath and 200 μm Ho:YAG laser fiber were used to clear this symptomatic, furosemide-induced stone.

Limitations and Complications

As ureteroscopy is becoming more prominent in the pediatric endourologist's armamentarium, complications need to be anticipated and unanswered questions addressed. *The most common complications involve unrecognized ureteral injury, including mucosal flaps and tears, perforation, false passage, and partial to complete avulsion.* Mitigating the damage by early recognition and temporizing with immediate discontinuation of the procedure and passage of a ureteral stent may avoid complications related to shear force injury on the ureter, ischemic damage, and extravasation of irrigant or urine. Injury can occur during introduction of the ureteroscope, or passage either antegrade or retrograde of instrumentation (guidewires, baskets, and dilators), especially in the area of an impacted ureteral calculus. Attempting to withdraw a basket-entrapped calculus too large for the ureter to accommodate can result in any of the above-mentioned injuries. In postpubertal children with an adult body mass, ureteroscopic access is technically similar to the adult population. However, in the prepubertal child, whether to attempt primary treatment without ureteral orifice dilation, perform dilation at the time of definitive therapy, or place a stent and allow the ureter to passively dilate prior to definitive therapy remains. Herndon et al. performed semirigid ureteroscopy (4.5 and 6.5 Fr) in 29 children with a mean age of 11 years for distal ureteral calculi. With no ureter actively dilated and only 14% of children prestented, the ureter was accessed in 100% of cases for a stone-free rate of 96%.[143] We can further validate this report with our own institutional experience utilizing 6.9 Fr flexible and 4.5 and 6.5 Fr semirigid ureteroscopy; however, it is our preference to sequentially dilate with the 8/10 coaxial dilator even in very young children. If we encounter difficulty, a stent is placed rather than dilated more aggressively. This approach appears to minimize the immediate risks and potential long-term complications, particularly in the management of upper tract calculi; however, it increases the number of children that require a second anesthetic and procedure to achieve stone-free status. Recent reports suggesting that up to 40% of pediatric patients will require at least two procedures to treat upper tract calculi imply that the likelihood of achieving a stone-free status after one ureteroscopic procedure may not be significantly better than with SWL.[138] Additional procedures were reported in more than half of the stones 6 mm or larger.[144]

The necessity of placing a stent postureteroscopy in all children is also debated. While the tendency in large series has been to leave a stent in place after ureteroscopic manipulation in a majority of children,[136] several authors have reported no acute or long-term sequelae despite leaving a postoperative stent in less than 20% of cases.[143] In our experience, the decision to place a postprocedural stent is made on an individual patient basis and is dependent on surgeon experience and degree of visible ureteral trauma at the conclusion of the procedure.

PERCUTANEOUS NEPHROLITHOTOMY

The safety and efficacy of PCNL for large stone burdens have been well established in adults. Initially, urologists were reluctant to perform PCNL in children due to concerns regarding the use of large instruments in pediatric kidneys, parenchymal damage and the associated effects on renal function, radiation exposure with fluoroscopy, and the risks of major complications, including sepsis and bleeding. Also a deterrent to performing PCNL in children was the potential resultant sequelae of hypothermia (i.e., coagulopathy) from prolonged exposure to irrigation. *With significantly accumulated experience, however, PCNL is currently being utilized as monotherapy and in combination with SWL (sandwich therapy) in children, achieving stone-free rates ranging from 68% to 100%*[15,145] (Table 27.3). *Although there is no current international consensus, relative indications for PCNL as the primary treatment modality in children include large upper tract stone burden (>1.5 cm), lower-pole calculi of >1 cm, concurrent anatomic abnormality impairing urinary drainage and stone clearance, and known cystine or struvite composition.*[77,95]

The earliest pediatric PCNL series were performed using standard adult-sized instruments. In 1985, Woodside et al. first reported on a series of seven patients (age range 5–18 years old) who were rendered stone-free without complications using adult percutaneous techniques and equipment.[166] Years later (1997), Mor et al.[167] reported on their pediatric PCNL series utilizing adult-sized instruments as well. These early series avoided performing PCNL in very small children (<5 years of age) due to concerns regarding parenchymal damage. *In contrast to these concerns, multiple series subsequently utilized adult-sized instruments and reported high efficacy rates with acceptable complication rates even when dilating a tract size as high as 30 Fr.*[164–168] *In fact, recent data have suggested that PCNL is possible in very young children using adult-sized*

TABLE 27.3 Outcomes of standard and mini-percutaneous nephrolithotomy in children

Study	No. children/ renal units	Mean age (years)	Max sheath size (Fr)	Energy source	Stone size (mm)	Transfusion (%)	PCNL stone-free rate (%)	Sandwich therapy (%)	Complications (%)
Mini-percutaneous nephrolithotomy technique									
Yan et al.[146]	20/27	3.6	16	P	18.5	0	85.2	7.4	Fever—15
Wah et al.[147]	12/23	4.8	16	HL, P	344 mm^2	0	90.5	0	Hydrothorax—8.3 Pneumonia—8.3 UTI—16.7
Resorlu et al.[148]	106	9.6	12–22	HL, US, P	23.7	6.6	85.8	9.4	Overall—17
Jackman et al.[149]	7/7	3.4	11	EHL	120 mm^2	0	86	0	None
Standard percutaneous nephrolithotomy technique									
Etemadian et al.[150]	38/45	8.4	26–30	US, P	29.3	2.6	67	15.8	Fever—21.1 Hyponatremia—2.6
Dogan et al.[151]	18/19	9.8	20–30	P	338 mm^2	22	73.7	27.8	Fever—33 Retroperitoneal extravasation—16.7 Perinephric hematoma—5.6
Nouralizadeh et al.[152]	20/24	3.1	26	P	33	5	79.2	13	Renal pelvis perforation—5 Urine leak—10 Fever— 15
Gonen et al.[153]	31/31	10.4	30	NA	929 mm^2	23	66.7	9.7	
Kapoor et al.[154]	31/31	9.6	24–30	NA	NA	6.6	83.9	6.4	Hematuria—23 Fever—45
Ozden et al.[155]	51/53	9.7	20 or 30	US, P	654 mm^2	17	73.6	13	Hydro- or pneumothorax—1.8 Urine leak—5.6
Samad et al.[156]	169/188	8.2	NA	NA	27.2 mm	4	59.3	34.5	Fever—42.8 Hyponatremia—0.1 Obstruction—0.1
Shokeir et al.[157]	75/82	6.6	30	US	178.6 mm^2	1.2	95	4.9	Urine leak—1.3 Fever—2.7 Renal pelvic perforation—1.3
Aron et al.[158]	19/19	4.2	24	P	972 mm^2	5	89	5.7	Fever—15.8 Ileus—5.3 UTI—5.3
Boormans et al.[159]	23/26	7.5	18	US	600 mm^2	4	81	23	Fever—8.7 Urosepsis—4.3 Steinstrasse—4.3
Dawaba et al.[160]	65/72	5.9	30	US	260 mm^2	1.5	86	7	Renal pelvic perforation—1.5 Fever—3.1
Mahmud and Zaidi[145]	29/30	3.8	NA	P	23.5 mm	6.9	60	40	Urethral stone—3.4 Ileus—3.4 Fever—34.5
Desai et al.[161]	56	9.1	20–24	EHL	337.6 mm^2	14.2	89.9	5.3	Urine leak—5.4
Salah et al.[162]	135/138	8.9	NA	US	507 mm^2	0.7	98.5	0	Urine leak—8

(*Continued*)

TABLE 27.3 *(Continued)* Outcomes of standard and mini-percutaneous nephrolithotomy in children

Study	No. children/ renal units	Mean age (years)	Max sheath size (Fr)	Energy source	Stone size (mm)	Transfusion (%)	PCNL stone-free rate (%)	Sandwich therapy (%)	Complications (%)
Holman et al.[163]	138	8.9	19–30	US	22.5	0.4	98.5	0	Fever—1.1 Urine leak—4 Ileus—4.7
Rizvi et al.[15]	62	NA	22	US	47	25.3	67.7	27.4	Open conversion—4.8 Fever—46.8 Urine leak—6.4 Hydrothorax—1.6
Zeren et al.[164]	55/62	7.9	30	US, EHL	16.8	23.9	86.9	1.6	Fever—29.8 Open conversion—1.6
Badawy et al.[165]	60	6	26–28	US	NA	3.3	90	1.7	Fever—8.3 Colon injury—1.7 Urine leak—3.3 Open conversion—5

Abbreviations: EHL, electrohydraulic lithotripsy; US, ultrasound; HL, holmium laser; P, pneumatic; NA, not available; UTI, urinary tract infection; VUR, vesicoureteral reflux.

equipment.[152] Investigations regarding the risk of renal damage in pediatric patients treated with PCNL have revealed that there is no significant risk of renal functional loss. Mor et al. performed radioisotope scans on 10 children before and after PCNL and found no change in differential function and no evidence of significant scarring.[167]

Despite early successes employing adult equipment, early efforts focused on developing technology to minimize percutaneous tract size without affecting PCNL efficacy. Jackman and Docimo developed a novel percutaneous access technique ("mini-perc") using an 11 Fr peel-away vascular access sheath and reported an 85% stone-free rate for 11 procedures in seven children with a mean age of 3.4 years and an average stone burden of 1.2 cm^2.[149] With a shortened tip of the inner vascular sheath to prevent renal pelvic perforation, mini-PCNL could now be safely performed in *preschool-aged children*. Mini-perc kits are now commercially available, ranging in size from a plastic disposable 11 Fr sheath (Figure 27.8) to a 16 Fr rigid metal sheath (Figure 27.9). *The benefits of minimal tract dilation include increased maneuverability, decreased blood loss, reduced complication rate, and shorter hospital stay. However, disadvantages including prolonged operative times, impaired visualization, and small nephroscope working channels limit this technique for very large stone burdens.*

Recent advancements in instrumentation, such as smaller nephroscopes (15–18 Fr) and less morbid renal access techniques, are reducing complications, hospital stays, and pain. As a result, PCNL has now replaced open surgery as the treatment of choice for a large stone burden of >2 cm in children of all ages. Recent reports comparing mini-PCNL with retrograde intrarenal surgery, however, are showing promise for ureteroscopy as an effective alternative to mini-PCNL for stone burdens between 1 and 3 cm.[148]

Four energy sources exist for intracorporeal lithotripsy, including electrohydraulic, pneumatic, ultrasonic, and laser probes. Electrohydraulic lithotripsy (EHL) sends current across a rigid probe (ranging from 1.9 to 9 Fr), creating a spark, which vaporizes irrigant into a cavitation bubble. Collapse of the bubble generates a shock wave to fragment the stone (Figure 27.10). Pneumatic ("ballistic") probes require direct contact with the stone and fragment via mechanical energy transmission with minimal risk to the surrounding urothelium. There are both rigid (0.8–2.5 mm) and flexible probes, with larger probes having greater efficacy. The Swiss Lithoclast has been the best studied. The Lithovac is a pneumatic probe that adds suction of stone fragments. Ultrasonic probes use high-frequency vibrations, come directly in contact with the stone to cause fragmentation, and with a central hollow core, allow for simultaneous suction of the fragments. Significant heat is generated by the ultrasonic probe, so care must be taken to avoid thermal injury to both the surgeon and patient. Pneumatic and ultrasonic probes run the least risk of urothelial and local tissue injury. Finally, the holmium:YAG laser is the most widely utilized laser in endourology, and is the only laser capable of fragmenting all stone types, yet it is relatively safe when kept at least 1 mm from urothelium. Photothermal energy

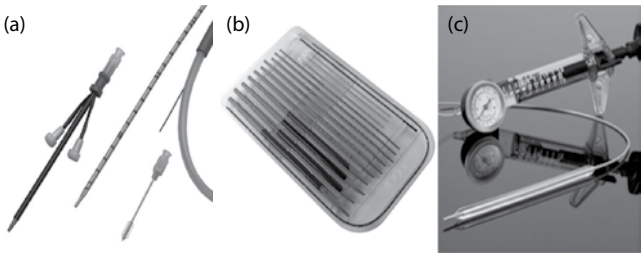

FIGURE 27.8 (a) Docimo Mini-Perc percutaneous nephrostomy set containing 11 Fr inner (removable) and 13 Fr outer sheath through which nephroscopy is performed via a flexible ureteroscope or pediatric cystoscope. (b) An Amplatz renal dilator set allows dilation up to 30 Fr for use of an adult rigid nephroscope. (c) A nephrostomy balloon dilator set contains 6, 8, and 10 × 15 mm balloons for dilation of the nephrostomy tract to 30 Fr and admission of adult nephroscopes. (From Cook Medical Inc., Bloomington, IN. With permission.)

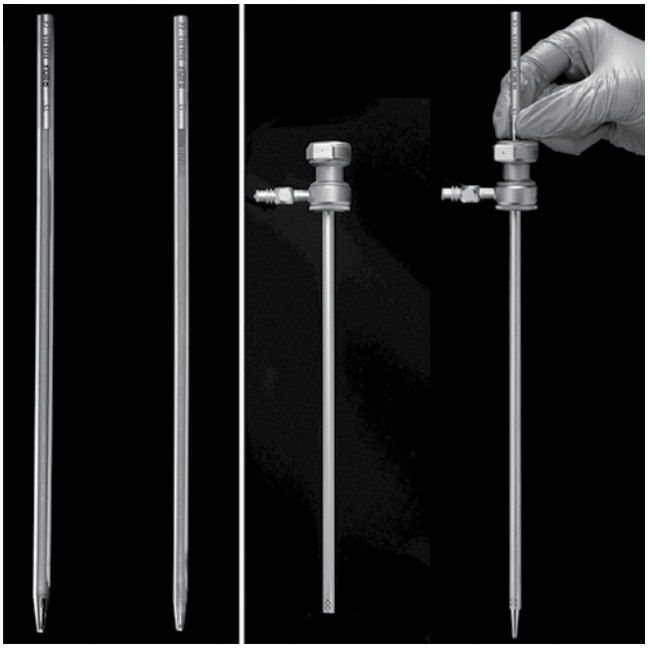

FIGURE 27.9 Smaller-caliber nephroscopes (15–18 Fr) advanced through reusable metal mini-sheaths help to minimize access tract size and reduce blood transfusion rates in pediatric patients. (Picture provided by Richard Wolf. Copyright © 2012, all rights reserved.)

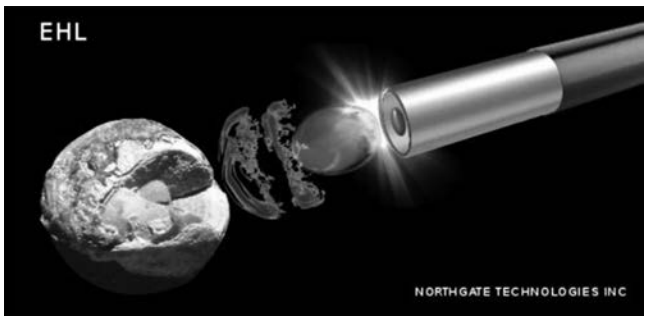

FIGURE 27.10 Four different energy sources are available for intracorporeal lithotripsy in children: laser, ultrasonic, pneumatic or ballistic, and electrohydraulic. EHL, depicted here, forms a cavitation bubble, which generates shock waves upon collapse of the bubble. Direct contact is not made with the probe, as the most effective lithotripsy occurs at a 1 mm distance. (From Northgate Technologies Inc., Elgin, IL. Reprinted with permission.)

is generated at a wavelength of 2100 nm, via laser fibers ranging in size from 200 to 1000 μm. Only 200 and 365 μm fibers can fit through a ureteroscope. Stones then require either complete dusting or basket extraction of fragments.[169]

Planning for PCNL in Children

Careful planning is required prior to embarking on PCNL in children. Films must first be reviewed scrupulously to determine if the stone is amenable to a percutaneous procedure. *Nephrocalcinosis in children, for example, may be confused with staghorn calculi, and the etiology and treatment are very different* (Figure 27.11). Infection is the most common causative agent in the formation of a staghorn calculus, and PCNL is a first-line therapy. The most frequent causes of nephrocalcinosis are hereditary tubulopathies and vitamin D intoxication. *Medullary sponge kidney is a renal malformation characterized by cystic anomalies of precalyceal ducts, which is frequently associated with nephrocalcinosis and stone formation.*[170] Nephrocalcinosis is most often not amenable to successful endourologic treatment because calculi are intraparenchymal, and thus outside the collecting system. Management is often medical and aimed at prevention of further nephrocalculi, a cause of worsening renal function. Medical prophylaxis for calcium-based stones, not necessarily associated with nephrocalcinosis, may also be very helpful in preventing stone recurrence and enhancing stone-free rates in children following surgical treatment, as has been demonstrated after pediatric PCNL.[171]

The risks of the PCNL must be reviewed with the consenting parent or guardian. *It must be understood that a percutaneous procedure carries risks that include, but are not limited to, bleeding requiring transfusion, delayed renal hemorrhage requiring angioablation, sepsis, pneumothorax, hemothorax, urothorax, incomplete stone treatment, and injuries to organs adjacent to each respective kidney.*

Every attempt should be made to treat a urinary tract infection and/or minimize bacteriuria prior to the procedure. A urine culture, with antibiotic sensitivities, should be checked 3 weeks prior to the procedure. Any positive culture requires a full course of antibiotics and repeat culture to confirm sterility. Three to five days of prophylactic antibiotics is recommended prior to the procedure, even with a negative preoperative culture. Broad-spectrum IV antibiotics (i.e., ampicillin and gentamicin) should be given at the time of the procedure.

All percutaneous procedures are performed using general anesthesia. *A warm operating room, warmed isotonic irrigation solution, short operative times (not to exceed 1.5 hours), proper draping, and monitoring of body temperature should decrease the incidence of hypothermia and hyponatremia.* After induction of anesthesia with the patient in the lithotomy position, a retrograde pyelogram is performed to outline the collecting system and an occlusive balloon or a 5 Fr open-ended ureteral catheter is left in situ to opacify the collecting system during percutaneous access. The patient is then repositioned in the prone position with the torso elevated at 30° from the table surface with a towel or gel roll.[95]

Circumstances that require special consideration involve children with spinal cord injuries and congenital anomalies, such as spina bifida. In these patients, positioning can be a challenge due to existing spinal hardware and limb contracture.[172] Patients who have had prior spinal surgery consisting of vertebral fusion or Harrington rod placement will have restricted spinal mobility, spinal curvature, and/or atrophic or contracted extremities. *As the result of scoliosis, lordosis, and or kyphosis, renal anatomy is altered. As a consequence, the risk of injuries to adjacent organs (i.e., pneumothorax) during percutaneous procedures increases.* Assessing the degree of mobility in the trunk and extremities is crucial in planning for

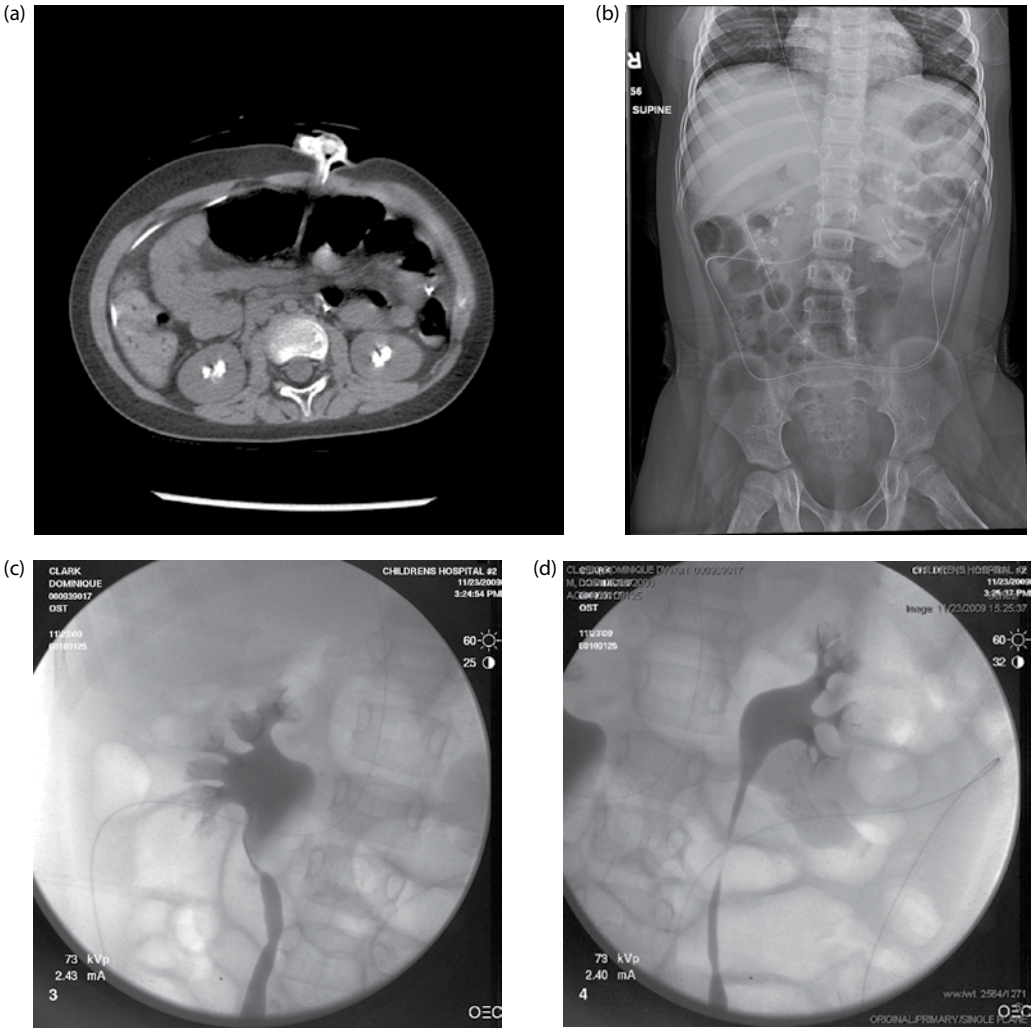

FIGURE 27.11 Nine-year-old boy with cerebral palsy and gross hematuria. CT scan demonstrated bilateral nephrolithiasis (a), thought to be staghorn calculi. Plain x-ray (b) and bilateral retrograde pyelograms (c and d) demonstrate nephrocalcinosis (white circles and black arrows) reflective of medullary sponge kidney. Subsequent metabolic workup revealed renal tubular acidosis with hypercalciuria.

PCNL in these patients. These patients must be placed in the most comfortable position possible without excessive contortion or flexion of the joints. Special attention must be paid to latex precautions in the myelomeningocele and bladder exstrophy populations, and as in all cases, proper padding of pressure points is mandatory.

Percutaneous Nephrolithotomy Technique in Children

After selection of the desired calyx, a 16- or 18-gauge spinal needle is placed with the assistance of fluoroscopy in the 30° position (Figure 27.12). When fluoroscopy is used, the collecting system is opacified through an open-ended ureteral catheter that has been inserted cystoscopically prior to positioning in the prone position (Figure 27.13). Alternatively, ultrasound guidance can be used to puncture the calyx of choice. The ideal tract is one that provides the shortest and most direct access to the stone (Figure 27.14). For complex calculi occupying multiple calices including the lower pole, supracostal posterior access is preferred to provide visualization of the superior calyx and pelvis, access to the pelvis and ureter, and straight access to the inferior calices, allowing easier manipulation of the working instruments and minimizing torque on the collecting system.[173] Following initial puncture, no attempt should be made to redirect the needle while it is located within the cortex of the kidney to avoid trauma. With the C-arm in the 90° plane, the depth and medial extension of the needle are checked. After access is confirmed with urine or irrigation return, a flexible guidewire is placed into the collecting system through the needle and directed down the ureter into the bladder. A small skin incision is made with a No. 11 scalpel, and 8 and 10 Fr coaxial dilators are passed over the guidewire into the collecting system. Once in place, an Amplatz Super Stiff™ guidewire is placed as a working wire.

Tract dilation can be performed by several techniques. Serial dilation with Amplatz dilators over working wires and subsequent sheath placement under fluoroscopic guidance is the most common technique employed. For

FIGURE 27.12 An initial mark can be placed on the back, using a metallic pointer under fluoroscopy to localize the desired posterior calyx. The desired calyx is localized with the C-arm at 0° and 30°, for AP and oblique orientation. The collecting system is visualized via retrograde contrast injection via ureteral catheter. Alternately, injection of air will localize the posterior-most calyx, as air bubbles will rise.

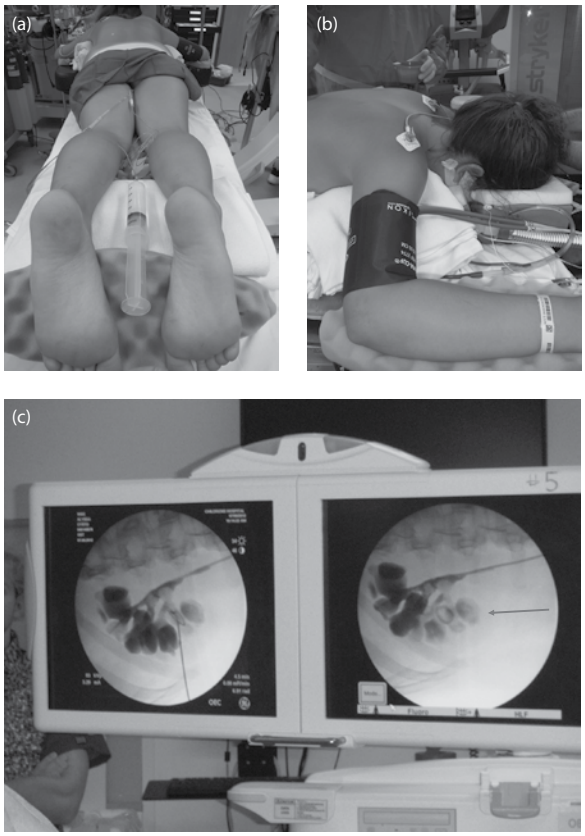

FIGURE 27.13 Fluoroscopic or ultrasound-guided renal access is performed at surgeon discretion. Patient positioning using the C-arm requires a sliding operative table. Flank and prone positioning are both adequate positioning options. Cystoscopy has been performed prior to prone positioning (authors' preference) for retrograde placement of a ureteral access catheter, for retrograde contrast injection (a). (b) Bilateral gel rolls are placed at the anterior axillary lines when prone. An axillary roll is used for older children in flank positioning. Careful axillary and ulnar padding (seen here) prevent brachial plexus and ulnar neuropathies. (c) A reference image is horizontally oriented and saved (on the right), demonstrating stone location throughout the procedure (arrow). The working fluoroscopic image is seen on the left, with wire coiling around the lower-pole stone.

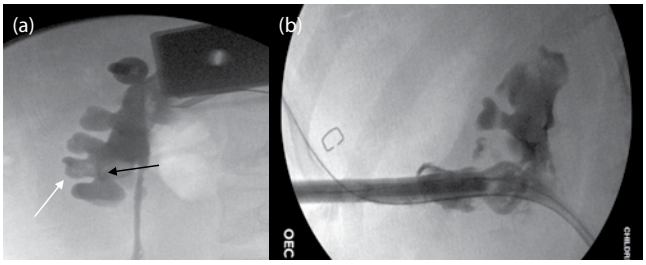

FIGURE 27.14 (a) Seven-year-old boy with two separate 7–9 mm stones within a lower-pole calyx (white arrow). Flexible ureteroscopy was attempted, but impossible due to a lower-pole infundibular-UPJ angle of >270° (black arrow). (b) PCNL was subsequently successful for complete stone clearance.

preschool-aged children and lower stone burdens, an 11 Fr peel-away sheath (Docimo Mini-Perc, Cook Urological Inc., Spencer, Indiana) and trocar are passed over the wire and through the calyx under fluoroscopic guidance. For balloon dilation, either the Bard X-Force or NephroMax™ High Pressure Nephrostomy Balloon Catheter (Boston Scientific, Natick, Massachusetts) may be used. Either will facilitate dilation of a 30 Fr tract at a pressure of 17 atmospheres. This technique permits dilation and sheath placement in a single step, thereby minimizing potential parenchymal trauma and bleeding from sequential dilation with rigid dilators. While the decision to proceed with mini-perc or dilation to a slightly larger (16 Fr) or standard (30 Fr) access sheath is individualized based on child's age, anatomy, and stone burden, familiarity with all the above techniques facilitates complete access with minimal morbidity.

Once access is obtained, nephroscopy and nephrolithotomy can be performed with a variety of energy sources for stone fragmentation. The outer diameter of nephroscopes ranges from 15 to 26 Fr, and a 15 Fr flexible nephroscope with a 6 Fr working channel has also been developed. In addition, 7 and 8 Fr offset cystoscopes with 5 Fr working ports and 7–9 Fr flexible ureteroscopes can be used through an 11 Fr access sheath with enough clearance to allow low-pressure irrigation.[77] Only the EHL probe or holmium laser fiber can fit through the narrow

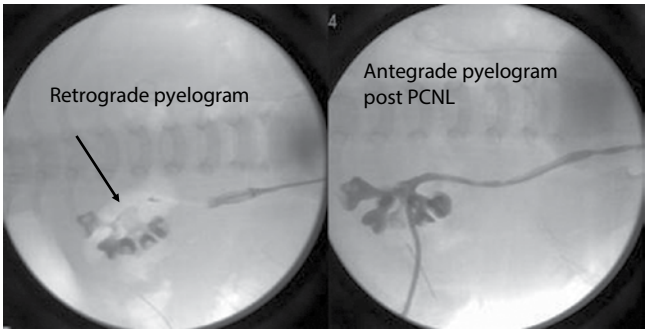

FIGURE 27.15 A retrograde pyelogram determines stone burden prior to renal access and can help localize the desired calyx for renal puncture. An antegrade pyelogram is routine to confirm nephrostomy tube placement and clearance of large stones after PCNL; if complete stone clearance is uncertain, second-look nephroscopy, delayed nephrostogram, and a low-dose CT stone protocol are acceptable options.

working channel in a pediatric cystoscope or ureteroscope during mini-perc. However, ultrasonic, pneumatic EHL, and the holmium laser are both accommodated through the adult nephroscope with a standard renal access tract. Individual preference is determined by availability and surgeon experience. Postoperative stenting and/or placement of a nephrostomy tube is both patient and surgeon dependent and varies between series. An immediate postoperative nephrostogram can be useful in determining renal drainage at the conclusion of PCNL (Figure 27.15). Similar to adult procedures, tubeless PCNL has theoretical advantages, including decreased postoperative pain and a short hospital stay, but currently data are limited in the pediatric population.[174]

Percutaneous Nephrolithotomy Outcomes

Recent large retrospective series of PCNL monotherapy have demonstrated high efficacy rates approaching 90%[161,164,168] (Table 27.3). In 56 children (mean age 9.1 years) with a mean stone burden of 337.5 mm^2, Desai et al. reported a stone-free rate of 89.8% utilizing EHL through a 14 Fr nephroscope and a 20–24 Fr sheath. Of these, 61% required multiple tracts and 45% were staged procedures. Findings demonstrated that the number and size of tracts were significantly associated with postoperative hemoglobin decrease (mean 1.9 g/dL) and overall transfusion rate (14%).[161] In 52 children with a mean age of 7.9 years and a mean stone burden of 282 mm^2, Zeren et al. reported an 87% stone-free rate using ultrasound and EHL for fragmentation and tract dilation from 18 to 30 Fr. Complications included postoperative fever (30%) and need for transfusion (24%). *Transfusion was associated with operative time, sheath size, and stone burden.*[164] In 135 children aged 8.9 years with a mean stone burden of 507 mm^2, Salah et al. reported a 98.5% stone-free rate utilizing ultrasound through a 26 Fr nephroscope. Complications were low (8% urine leak rate and 0.7% transfusion rate), with only one patient requiring a second procedure.[162] In a recent series of 46 children with a mean stone burden of 332 mm^2, Bilen et al. reported an 88% stone-free rate using EHL, ultrasound, and the holmium laser. When stratified by tract size (14, 20, and 24 Fr), efficacy rates were similar in all groups, but there were no complications or transfusions in the 14 Fr tract group.[168]

In an effort to reduce the number of tracts and associated morbidity, some centers have chosen to follow primary PCNL with adjunctive SWL therapy to clear RFs. In a small series of 29 children with a mean age of 3.8 years and a mean stone burden of 2.4 cm, Mahmud and Zaidi reported a 60% stone-free rate after PCNL monotherapy using EHL through a 17 Fr angled nephroscope. Only one tract was used in all patients, and after SWL sandwich therapy, the stone-free rate increased to 100%.[145] In a larger series of 169 children with a mean stone burden of 3.1 cm, Samad et al. reported a 59% monotherapy stone-free rate with 96% of cases performed through a single tract. Approximately one-third (34.5%) of primary failures were treated with SWL; the cumulative stone-free rate in all patients was 93.8%, with a 3.6% transfusion rate.[156] When stratified by age, anatomy, bilaterality, and renal function, stone-free outcomes were equivalent in all groups. The decision to follow PCNL with SWL is related to operator experience with percutaneous technique and available technology. *It is our preference to perform a second-look nephroscopy through the original tract to ensure stone-free status during the initial hospital admission rather than progress to SWL sandwich therapy.* Endoscopic surveillance during the initial procedure can determine the need for second-look nephroscopy without relying on additional imaging and the associated risks of radiation exposure.[175] With continued improvement in technology and technique, the indications for PCNL in children will continue to increase. Technically challenging in nature, surgeon experience with PCNL is paramount in developing individualized treatment plans to optimize efficacy with minimal morbidity.

LAPAROSCOPIC AND ROBOTIC-ASSISTED PYELOLITHOTOMY

Treatment of large stone burdens in children is technically challenging, often requiring multiple procedures. Laparoscopy and robotic-assisted laparoscopy has been utilized successfully in adults for the treatment of calculi during the concomitant treatment of UPJ obstruction and in the primary treatment of staghorn calculi. Small series utilizing these techniques in children have only recently been described. In eight children (mean age 4 years) with a mean stone burden of 2.9 cm undergoing transperitoneal laparoscopic pyelolithotomy, Casale et al. reported a 100% intraoperative success rate, a mean hospital stay of 2.15 days, and a mean operative time of 1.6 hours, with no major complications.[176] In the first report of robotic-assisted laparoscopic pyelolithotomy, Lee et al. described their experience in five patients, four with cystine staghorn calculi refractory to PCNL and SWL and one with calcium oxalate calculi and concurrent UPJ obstruction. Of these cases, four were completed robotically, with one patient having a residual 6 mm lower-pole stone and one patient requiring conversion to an open procedure. The mean operative time in this series was 315 minutes, the

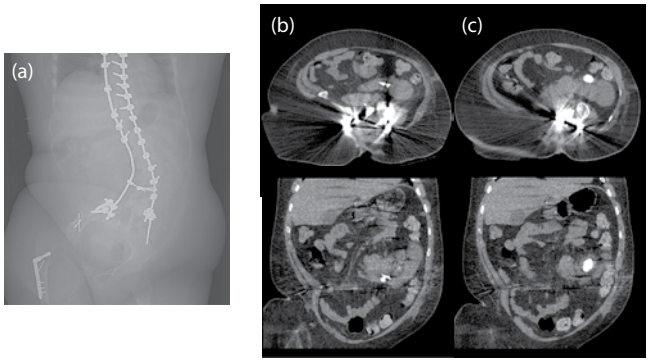

FIGURE 27.16 (a) Stones overlying spine not seen on x-ray due to body habitus: 1.8 cm in left lower pole near isthmus and 3.1 cm in left renal pelvis in horseshoe kidney. (b and c) When faced with the inability to access stones percutaneously (for example, overlying spinal hardware in a horseshoe kidney) and high stone burden, minimally invasive or open pelviolithotomy is an efficient option to multiply staged SWL or ureteroscopy.

mean estimated blood loss was <20 cc, and the mean hospital length of stay was 3.8 days.[177] These early experiences demonstrate that laparoscopic pyelolithotomy is feasible, safe, and efficacious as an alternative to open pyelolithotomy in children and warrants further study. However, due to their demanding technical nature, these procedures will likely be limited to endourologic management failures or renal anatomy, which prohibits ureteroscopic and percutaneous intervention. For example, vertebral abnormalities, such as severe scoliosis or spinal hardware, may obstruct access to a horseshoe kidney with a large amount of stone burden, as seen in Figure 27.16.

PERCUTANEOUS CYSTOLITHOTRIPSY FOR BLADDER STONES

Bladder stones are more often found in children from developing countries and are thought to be related to malnutrition in the absence of anatomic abnormality. It is thought that diets low in animal protein and phosphorous (breast milk as opposed to cow's milk), in addition to vitamin A deficiency, are contributory.[178] *Bladder stones from children in these developing countries are most often composed of ammonium acid urate*. In contrast, among children from industrialized nations, bladder stones are most often found in those with spinal cord injuries or congenital abnormalities, such as spina bifida. Very often, these children have undergone augmentation cystoplasty and/or manage their bladders by clean intermittent catheterization. *It has been reported that up to 50% of those children with reconstructed bladders will develop a bladder stone in their lifetime.*[179] *Urinary stasis, bacterial colonization or infection with urea-splitting organisms, retained mucous, and foreign bodies can all contribute to the formation of bladder stones, the majority of which are struvite. Recently, dextranomer/hyaluronic acid (Deflux®) has been demonstrated in a trigonal and distal ureter distribution following endoscopic treatment of vesicoureteral reflux*. While uncommon, this is now in the differential diagnosis of bladder and distal ureteral stones for patients providing a history of Deflux injection, who have lower-density lesions (median 193 Hounsfield units) on CT than is expected of calculi[180] (Figure 27.17).

Open cystolithotomy has been the traditional modality to treat bladder stones. Transurethral cystolithotripsy is an alternative, although not ideal in the pediatric population. In children, a smaller-caliber urethra limits effective treatment of large bladder stone burdens. Percutaneous cystolithotripsy, however, is now utilized worldwide with the advantage of shorter hospital stays, smaller scars, and less indwelling catheter time postoperatively.[181] Presently, percutaneous cystolithotripsy is the preferred method to treat bladder stones that have formed in reconstructed bladders.[182] In developing countries as well, percutaneous lithotripsy has become the first-line treatment modality to address bladder stones in bladders that have not been augmented. Salah et al. reported on their experience with cystolithotripsy in 155 children from Pakistan and Yemen with a mean age of 4.5 years and average bladder stone burden of 2.3 cm (range 0.7–4 cm). All children were treated safely and successfully using a 26 F nephroscope through a 30 F sheath placed through a 1 cm suprapubic incision.[183]

Percutaneous cystolithotripsy has also been used effectively in infants of less than 1 year of age to clear bladder stones. Gan et al. reported on their experience using a 16 F peel-away sheath with a ureteroscope to treat bladder stones with an average size of 1.4 cm in 15 boys with a mean age of 8.2 months.[184]

Percutaneous cystolithotripsy in children may be performed under ultrasound or fluoroscopic guidance and is most often an outpatient procedure. With either modality, the bladder is first filled to capacity with water or contrast, respectively. The child is placed in the Trendelenburg position to minimize the risk of bowel injury during access and tract dilation or formation. An 18-gauge needle is

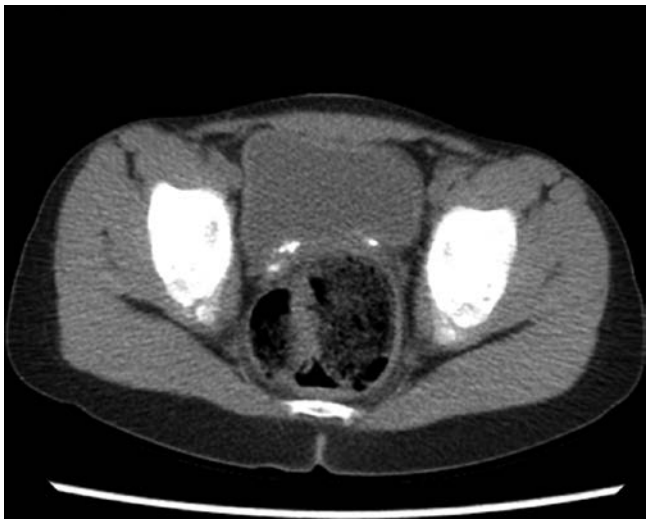

FIGURE 27.17 False-positive CT scan for distal ureterolithiasis in a 7-year-old patient with a history of bilateral subureteric Deflux injections. Median densities up to 193 Hounsfield units are reported for Deflux implants on noncontrast CT. Abdominal x-ray does not visualize these implants. Patient history and lower-density appearance are keys to an accurate diagnosis.

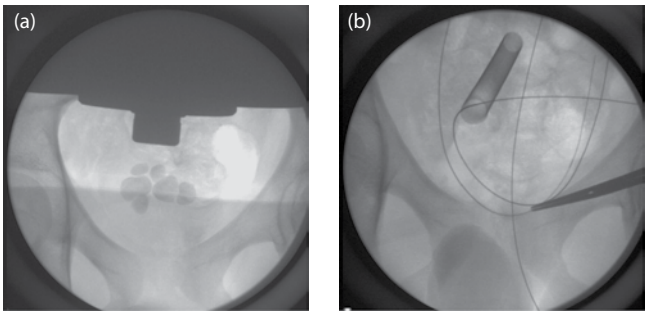

FIGURE 27.18 (a) Bladder stones in a spina bifida patient post-ileocystoplasty. (b) An Amplatz 30 Fr sheath and rigid nephroscope (seen here) or 10 mm laparoscopic trocar can be placed into the bladder, facilitating percutaneous ultrasonic lithotripsy or basketing. Referring to recent cross-sectional imaging is important if the patient has had prior bladder or bowel surgery. Loops of the bowel may overlie the bladder and be injured with percutaneous access. Catheter placement per Mitofanoff or Monti is critical to prevent injury to a continent catheterizable channel.

placed into the distended bladder midline, one to two finger breadths above the pubic bone. Once proper placement is confirmed with return of fluid, a wire is passed through the needle into the bladder. A tract may then be established reflective of stone diameter and child size. Most often, a tract is established with a balloon dilator to accompany a 30 F sheath. Amplatz dilators may also be used. A 26 F nephroscope is used to extract stones of <1 cm with a rigid stone forceps, or an ultrasonic lithotriptor may be used to fragment stones of >1 cm. At the conclusion of the percutaneous cystolithotripsy procedure, a Foley is left per urethra or per continent catheterizable stoma for 1 week. The rectus fascia defect is closed with a 2-0 vicryl suture (Figure 27.18).

SILENT OBSTRUCTION AND OTHER CONSIDERATIONS

Silent ureteral obstruction, evaluated in 506 adult patients, was associated with reduced renal function at the time of stone diagnosis and no further deterioration after stone clearance.[185] While similar pediatric data are not available, *silent obstruction is a relative indication for surgical intervention in children in order to preserve renal function and prevent further deterioration.*

DETERMINATION OF STONE-FREE STATUS

To date, there is no standardized method of defining stone-free status following definitive therapy. Similar to adults, the presence of RFs in children has been associated with inferior outcomes and increased stone recurrence.[75,186] Dincel and colleagues recently evaluated 49 children retrospectively following ureteroscopy to determine an efficient imaging regimen for the identification of clinically significant stone fragments.[190] At initial follow-up, three stone fragments were found to have migrated to the kidney, requiring further surgery, and six kidneys were found to be hydronephrotic, although five of six responded favorably to medical expulsive therapy or observation. Unfortunately, renal ultrasound alone was only useful for the detection of postoperative hydronephrosis with 85.7% and 97.7% sensitivity and specificity. In this series, the authors found the combination of renal ultrasound and abdominal plain film to be adequate for postoperative surveillance of hydronephrosis and stone fragments, respectively. Weizer and colleagues recommend a regimen of IVP, spiral CT, or renal ultrasound within 3 months of surgery to survey for silent obstruction, which occurred in 2.9% of their adult series.[187] However, proponents of earlier surveillance recommend imaging within 6 weeks of surgery due to the risk of silent obstruction with incipient renal damage. *To limit the risk of chronic damage in the pediatric kidney, surveillance renal ultrasound within 6 weeks of surgery is recommended.*

Balancing the risks of radiation exposure for post-treatment stone detection and the risks of anesthesia for secondary procedures is a challenging dilemma for contemporary pediatric endourologists. Ultimately, if stone fragments are seen on plain film, CT does not provide additional useful information.[188] In addition, maximizing intraoperative fragment detection by direct visualization in URS and PCNL and continued development of high-resolution real-time fluoroscopy may result in less reliance on postoperative imaging. Advancements in flexible ureteroscopes and nephroscopes, transitioning from fiber-optic to digital technology and with "chip on the tip" technology, should maximize image quality and decrease the need for second-look surgery or sandwich therapy.[172] Since ionizing radiation use in children is still subject to the as low as reasonably achievable (ALARA) principle, use of stone protocol CT scans for postoperative surveillance is not routine and should be based on suspicion for RFs. Surveillance CT should be individualized by age, anatomy, stone burden, and underlying metabolic abnormalities.

CONCLUSIONS

Evolution of technique and miniaturization of instruments have changed the management of pediatric stone disease. However, despite encouraging results, concern remains regarding the safety of the endourologic treatment in smaller patients and its subsequent effects on the developing kidney. While SWL is still considered first-line therapy for upper tract calculi of <1.5 cm, evidence is accumulating that ureteroscopy with laser lithotripsy and stone basketing may be more efficacious and reduce retreatment rates for upper tract stone disease in children. Ureteroscopic stone extraction is also becoming recognized as similarly efficacious compared with mini-PCNL, with potentially fewer side effects. While PCNL remains the most effective technique for large upper tract stone burdens, there are now reports of laparoscopic and robotic-assisted laparoscopic pyelolithotomy in major pediatric academic centers with extensive laparoscopic and robotic experience. Prospective studies designed to determine "the preferred" endourological approach to upper tract calculi would provide useful information.

In this regard, individual surgeon experience and comfort level will weigh heavily in choosing a treatment modality. In addition, standardized protocols for diagnostic imaging, renal monitoring with conservative therapy, and postoperative surveillance are needed. Pediatric urologists will have to monitor the advances in minimally invasive lithotripsy techniques, as we aim to minimize morbidity and preserve renal function in children at high risk of stone formation into adulthood.

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MULTIMEDIA FILES AVAILABLE ONLINE (www.crcpress.com/cw/Docimo)

VIDEO 27.1 Mini-Perc technique.

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CHAPTER
28

Renal Parenchymal Imaging in Children

Daniel B. Herz

INTRODUCTION

Traditionally, imaging of the renal parenchyma is useful to determine if there is acute urinary tract infection (UTI) that involves the parenchyma, the presence of renal cortical scarring and differential function, the presence and character of a mass or cyst, the presence of congenital dysplasia, the presence and burden of nephrocalcinosis, and the extent of renal trauma, as well as to evaluate gross or microhematuria. In addition, more recently, parenchymal imaging is useful in the *top-down approach* to determine the true overall renal risk of a child with UTI. This has gained resurgent interest after several studies have shown that this can be pivotal in determining the clinical significance of vesicoureteral reflux (VUR).[1–3] Ultrasound (US), in general, is the primary initial imaging modality of the renal parenchyma in infants and children. It has essentially replaced intravenous pyelography (IVP), and is found to be more cost-effective and safer than computed tomography (CT) and magnetic resonance imaging (MRI). Renal scintigraphy, however, has maintained its usefulness because it is used to determine differential function, excretory function, and parenchymal integrity.

US uses sound waves that are above the audible range of normal human hearing of 20 kHz. Medical US probes typically operate at frequencies of 2–18 MHz. The choice of frequency to use to image different parts of the body is based on a trade-off between image resolution and depth of penetration into the body. Lower-frequency sound waves penetrate deeper into the body. Higher-frequency sound waves have lower wavelengths and higher attenuation coefficients; thus, they are absorbed more readily by tissues and do not penetrate as deep, but the images have better resolution. Imaging the kidney will typically use lower frequencies, unless imaging an infant, where higher-frequency probes will be used because deeper penetration is not needed. Higher-frequency sound waves can also detect and reflect sound off smaller structures and, for this reason, are also better suited for the pediatric application. The sound wave is typically produced by a piezoelectric transducer that is made of ceramic that vibrates or "rings" when contacted by short electrical pulses produced by the machine itself. The sound is then focused in an array that is based on the shape of the transducer, which is then transmitted through a water-based gel on the child's skin. Sound is then deflected and reflected based on the density of tissues it contacts. The reflected sound wave or "echo" is picked up and then vibrates the transducer, which is converted to an electrical pulse. This pulse is then processed into a digital image. To create the two-dimensional (2D) image, the US machine must also determine how long it took for the echo to be received after it was transmitted (the greater the time, the deeper the image), how strongly the echo was reflected back (the stronger the reflection, the brighter the image), and the focal length of the object reflecting the sound wave back. Based on these three determinations, the machine creates pixels of different intensities and positions. This "sonogram" image is the digital construct of the pixels created by sound wave reflected back to the transducer by that particular body organ or structure. Solids and gases have the greatest acoustic impedance, and therefore will be almost 100% reflected back and show up as a bright white image.

For the vast majority of medical imaging, US images are 2D. Commonly, a specialized probe that mechanically scans a conventional 2D image transducer is used. Doppler US is used to study blood flow and muscle motion. The different detected speeds are represented in color for ease of interpretation. The *Doppler effect* assesses whether fluid, usually blood, is moving toward or away from the probe. By calculating the frequency shift of a particular sample volume, its velocity and direction can be determined and visualized. This is particularly useful in urology to determine the absence of obstruction in a ureter, or vascular flow in a kidney. The Doppler information is often displayed graphically using a spectral Doppler, or as an image using a color Doppler (directional Doppler) or power Doppler (nondirectional Doppler). Most modern US machines used in medical technology use the color red to indicate flow toward the transducer and blue away from the transducer. Because at any one angle the kidney has arterial and venous blood flow that can be both toward and away from the transducer, the sonographer and urologist must understand the underlying acoustic physics of color Doppler and the physiology of normal and abnormal blood flow in the human body.[4–6]

The strengths of US lie in its ability to image muscle, soft tissue, and bone surfaces, as well as show the structure of organs. It is also particularly useful for delineating the interfaces between solid and fluid-filled spaces. It can also render "live" images, where the operator can readily and dynamically select the most useful section for diagnosis and documenting changes over time. Live images also allow for US-guided biopsies or injections, which can be cumbersome with other imaging modalities. US has no

known long-term side effects and rarely causes any discomfort to the patient. US equipment is widely available, relatively inexpensive, and comparatively flexible, and easily carried scanners are available so that examinations can be performed at the bedside. US is generally considered to be the safest imaging modality.[7–15]

The weakness of US devices is that they have trouble penetrating bone and gas, and they perform very poorly when there is a gas or bone between the transducer and the organ of interest. Overlying rib and/or gas in the gastrointestinal tract often makes US scanning of portions of the kidney difficult, especially in obese children, even at low frequency. Furthermore, using a lower-frequency transducer to compensate for body habitus and increased thickness of the subcutaneous fat often yields lower-resolution poorly diagnostic images. US is also very operator dependent. A high level of skill and experience is needed to acquire good-quality images and make accurate diagnoses, especially in pediatric and prenatal fetal applications. One further limitation is that there is no scout image, as there is with CT and MRI, and so there is no comparison of tissues to baseline.

Normal Kidney Ultrasound

There are normal differences in the imaging characteristics of the kidneys between newborns, infants, and younger children and older children. In newborns and infants, the renal cortex is much thinner, with larger, more hypoechoic-appearing medullary pyramids, which can be attributed mostly to dilute or poorly concentrated urine in the distal tubules and collecting ducts. This appearance of the medullary pyramids can be misinterpreted as hydronephrosis or caliceal dilation to the inexperienced clinician. In the neonate, a transient increase in the echogenicity of the medullary pyramids can also be seen, and results from precipitation or protein deposits in the tubules, known as Tamm–Horsfall proteinuria. Dehydration and administration of hyperosmolar contrast agents can make this phenomenon worse. However, this is considered to be benign and self-limited.[16–19]

In the first 2–3 months of life, the cortex is thinner and can appear hyperechoic or echogenic compared with the adjacent liver or spleen. It has been suggested that this is due to the increased number of glomeruli in the renal cortex, as well as a larger number of the loops of Henle (~20%) being situated in the cortex compared with in the older child.[20] This phenomenon can be normal and persist up to 6 months of age.[21–24] However, if the echogenicity of the renal cortex after 2–3 months is much brighter than the liver or spleen, this is a sensitive marker for underlying parenchyma medicorenal disease. Two other phenomena occur in the newborn kidney that might be misinterpreted or mimic pathology. The first results in a fusion line between two areas of primitive blastemal, which results in an echogenic stripe of nonparenchymal extrarenal fatty tissue that often courses obliquely through the upper pole of the kidney. This is called the interrenicular line or Odonno's sulcus.[25,26] This should not be misinterpreted as a parenchymal scar. Due to the relative thin newborn cortex, a column of Bertin hypertrophied segment of parenchyma can be easily misinterpreted as a renal mass. This can easily be cleared up by CT or MRI; however, these studies in newborns and young infants are quite sensitive to motion artifact and require anesthesia sedation and intravenous injection of potentially nephrotoxic contrast agents.

Any process that disrupts the normal parenchymal architecture is likely to change the acoustic characteristics of the tissue. Alterations in renal perfusion, cellular infiltration, and interstitial fluid level are common in acute pathology and will likely change the acoustic interfaces and the echogenicity of the kidney without disrupting overall architecture (Figure 28.1). However, interstitial fibrosis and histologic disruption and nephron disorganization are common in chronic pathology and are very likely to alter normal architecture and cause changes in the acoustic interfaces between the renal cortex and medulla. This change results in poor corticomedullary differentiation, the hallmark of what is broadly referred to in pediatric renal imaging as *medicorenal disease* (Figure 28.2).[27–31] Renal size or linear measurement may also change with disease states in the child. A large echogenic kidney usually suggests acute cellular infiltration and edema. Smaller highly echogenic kidneys usually indicate a chronic condition with renal atrophy or loss of nephron function. Surveillance of renal growth by serial renal size measurement is a valuable way to establish the health of the kidneys over time.[21,27,32,33] Measuring the

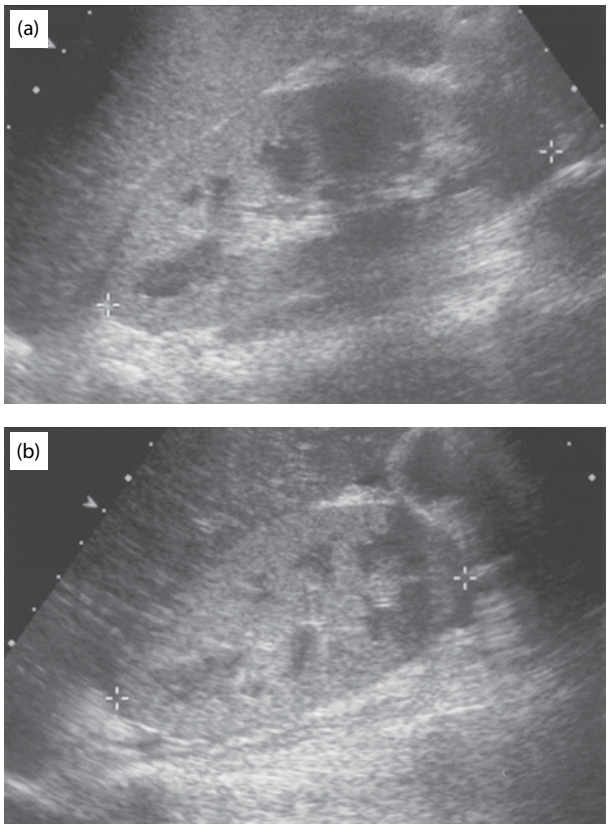

FIGURE 28.1 A 7-year-old boy with toxic shock syndrome presenting with scalded skin syndrome and acute oliguric renal failure. Ultrasound shows both kidneys are markedly enlarged with diffusely echogenic cortex. However, the pyramids remain hypoechoic and are easily identified. (a) Ultrasound: longitudinal view of the right kidney (length 9.3 cm). (b) Ultrasound: longitudinal view of the left kidney (length 9.3 cm).

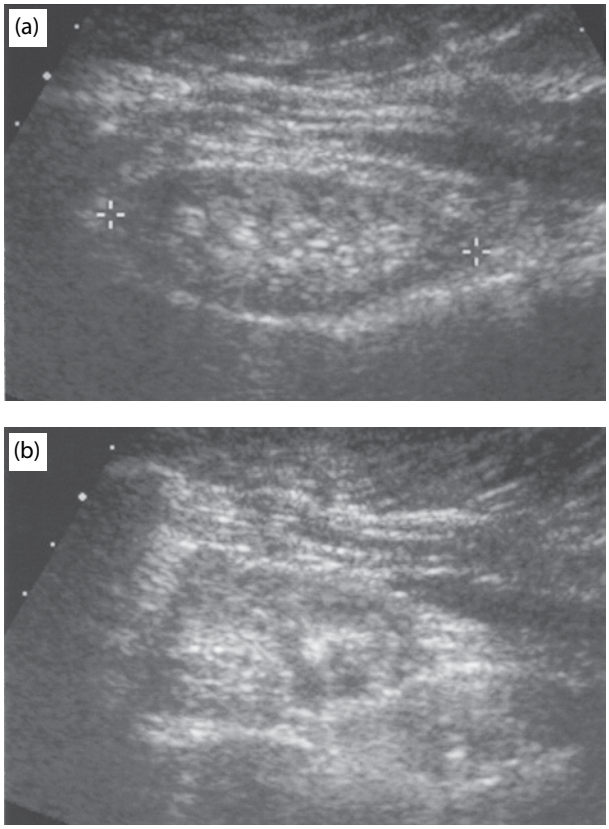

FIGURE 28.2 A 16-year-old boy with chronic medical renal disease and renal insufficiency on hemodialysis. Ultrasound of the kidneys shows that both kidneys are small with diffusely echogenic parenchyma and no visible corticomedullary differentiation. (a) Ultrasound: longitudinal view of the right kidney (length 6.7 cm). (b) Ultrasound: longitudinal view of the left kidney (length 6.8 cm).

resistive indices of the kidney in a young child is not often performed, and some question its value. However, in general, processes that cause obstruction of the collecting system, interstitial fibrosis, or obstruction of venous outflow will cause a rise in the resistive index. Both acute and chronic pathology that cause a reduction in the arterial inflow will be associated with a reduced resistive index.[21,27,31,34]

RENAL INFECTION

Acute Pyelonephritis

Currently, the initial study of a child with a febrile UTI suspected of having acute pyelonephritis (APN) is a renal US. Findings of acute infection are localized or generalized enlargement of the kidney due to acute cellular infiltration and interstitial edema (Figure 28.3a). There is usually thickening of the lining of the collecting system, and the renal parenchyma initially appears hyperechoic with loss of normal corticomedullary differentiation. Depending on the stage of infection and the presence of tissue ischemia, the parenchyma may appear hypoechoic.[35–45] Doppler or power Doppler examination of the kidney in the early stage would reveal hypervascular flow. As inflammation becomes worse and necrosis begins, the renal perfusion in affected areas would then change and appear hypovascular. Proponents of early US argue that pelviectasis that results from endotoxin in the urinary system or blood, desquamated cellular and crystalline debris, or frank purulent material in the collecting system will alert the clinician to those that are at risk for having underlying obstruction or VUR. Recently, however, some have begun to question the utility of US after the onset of febrile UTI. In 2003, Hoberman et al.[46] found that US was of limited value in children with their first acute febrile UTI because the abnormalities found in the 12% of 309 children did not change the immediate management. He attributed this to the assumption that in the modern era of prenatal US, almost all clinically significant renal abnormalities due to obstruction or VUR would be diagnosed before the onset of infection during the postnatal workup for prenatally detected abnormalities. However, despite this report, in 2010, the American Academy of Pediatrics (AAP) came out with new guidelines that recommended an US in children even after the first febrile UTI.[47]

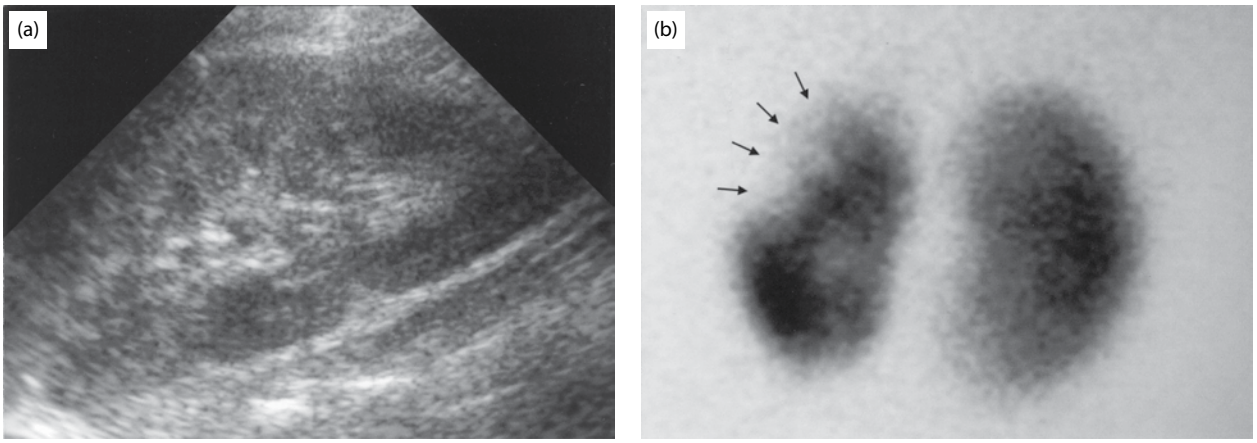

FIGURE 28.3 A 7-year-old girl with fever and left flank pain due to acute left pyelonephritis. (a) Ultrasound: longitudinal view of the left kidney (length 10.3 cm) shows that the upper half of the left kidney is enlarged and echogenic and appears somewhat bulbous compared with the lower pole. (b) ^{99m}Tc DMSA renal cortical scintigraphy (posterior view) confirms the presence of a large perfusion defect in the upper half of the left kidney (arrows).

Since US findings are neither sensitive nor specific, and changes in renal size and contour, as well as changes in parenchymal echogenicity, are often too subtle to detect prospectively during acute infection,[38,41,48,49] some have advocated the use of dimercaptosuccinic acid (DMSA) renal scintigraphy in the early stages of infection to diagnose APN. This so-called top-down approach relies on the sensitivity and specificity of a triangular wedge-shaped area of reduced cortical uptake of radiotracer (Figure 28.3b) that is characteristic during acute infection, as opposed to no cortical uptake in the area of a chronic previous renal scar.[41,48,50–53] The postulate behind the top-down approach is that a more reliable diagnosis of APN would establish a more accurate renal risk over time and, by doing so, identify those with clinically significant VUR. Then, voiding cystourethrography (VCUG) could be utilized exclusively in those with a positive scan who are at the highest renal risk. In the past, when a DMSA scan was performed after 3–6 months, when the majority of children at high renal risk have a normal scan, many children with clinically significant VUR and other nonrefluxing children at higher renal risk were "missed" because VCUG was not performed and measures to prevent further APN were not embarked on. Because of this, some have argued for a DMSA scan in the acute setting to determine who is at highest renal risk because they have radiographic evidence of renal inflammation. Indeed, when put to the test in recent years, it has been shown that a DMSA renal scan in the early phases of acute infection can identify almost all children with clinically significant VUR, identify children with and without VUR who have the greatest potential for renal scarring, and identify a cohort of children at greater risk for recurrent pyelonephritis and renal scarring based on comorbid bladder and bowel dysfunction.[1–3]

The practical role of CT and MRI in APN is less clear. Prior studies have shown a sensitivity similar to that of the gold standard DMSA.[50,52,53] On contrast-enhanced CT scan, APN appears as segmental areas of decreased or uneven parenchymal enhancement, with patchy areas of edematous margins that are most common in the poles of the kidney (Figure 28.4).[41,45,53–56] On postgadolinium contrast MRI T1-weighted images, areas of acute inflammation show reduced contrast enhancement; however, with T2 and inversion sequences, areas of acute inflammation remain bright, while healthy enhancing parenchyma has reduced signal intensity.[35,52,53,56–59] In several recent comparisons of diffusion-weighted (DW) versus the traditional gadolinium contrast-enhanced MRI, DW confirms the presence of APN with comparable sensitivity and specificity. The authors note that DW is a rapid, comprehensive, less expensive alternative magnetic resonance modality to traditional contrast-enhanced MRI that could obviate the need for contrast for the diagnosis of APN. Figure 28.5 shows that only the nonspecific finding of renal enlargement can alert the clinician to the presence of APN.

From the studies that have been published comparing the different diagnostic imaging modalities in APN, renal US, even with power Doppler imaging, seems to be the easiest and least expensive initial study to obtain in children suspected of having APN; however, it is the least sensitive. DMSA, contrast-enhanced abdominal CT scan, and contrast-enhanced abdominal MRI, on the other hand, all have comparable sensitivities (>90%). Since the kidneys are relatively radioresistant compared with other solid organs and gonads, and the kidneys take up the entire dose of the ^{99}mTc-DMSA, DMSA has an advantage over CT scan, where the entire abdomen receives the dose of radiation. MRI has the advantage of no radiation exposure but is very expensive. All three modalities are motion artifact sensitive, so all three require sedation in the younger child. DW MRI seems to have the most promise for the future because it offers multiplanar sensitive imaging without radiation exposure, and since it is a rapid study, sedation risks, as well as the associated prohibitive costs, are mitigated.[60–63]

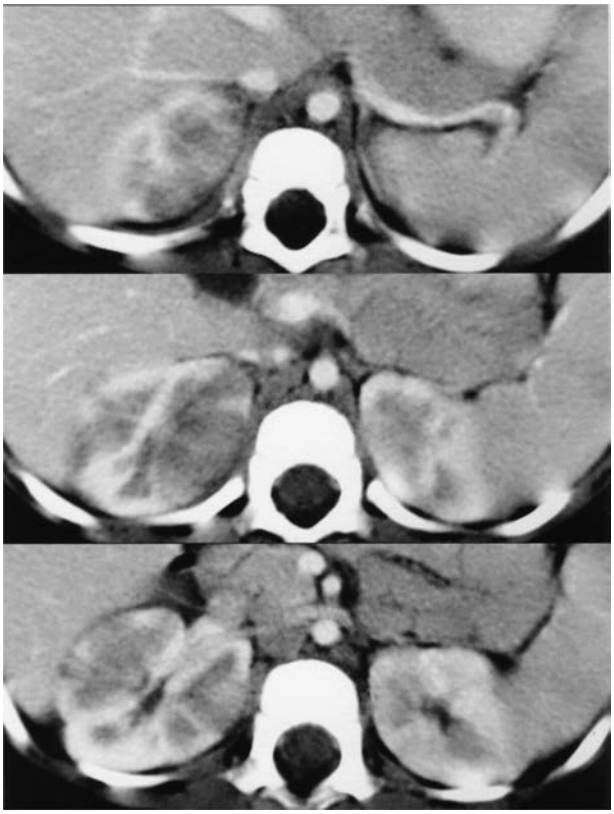

FIGURE 28.4 An 18-month-old girl with bilateral acute multifocal pyelonephritis, presenting with high fever and febrile seizure. Contrast-enhanced CT shows multiple wedge-shaped, low-attenuation, non-enhancing lesions in both kidneys.

Fungal Pyelonephritis

This form of pyelonephritis is usually associated with sepsis and is common in newborns and older children with indwelling urinary catheters, as well as immunocompromised children. Fungal septicemia from urinary fungal infection has an associated 50% mortality in children. Early diagnosis and aggressive treatment are essential. US is usually diagnostic since fungus balls are hyperechoic and do *not* shadow. On CT scan, focal areas of fungal pyelonephritis and fungal abscesses appear similar to bacterial pyelonephritis and abscess with heterogeneous areas of low attenuation (Figure 28.6). *Candida albicans* is the most common organism.[58,64–67]

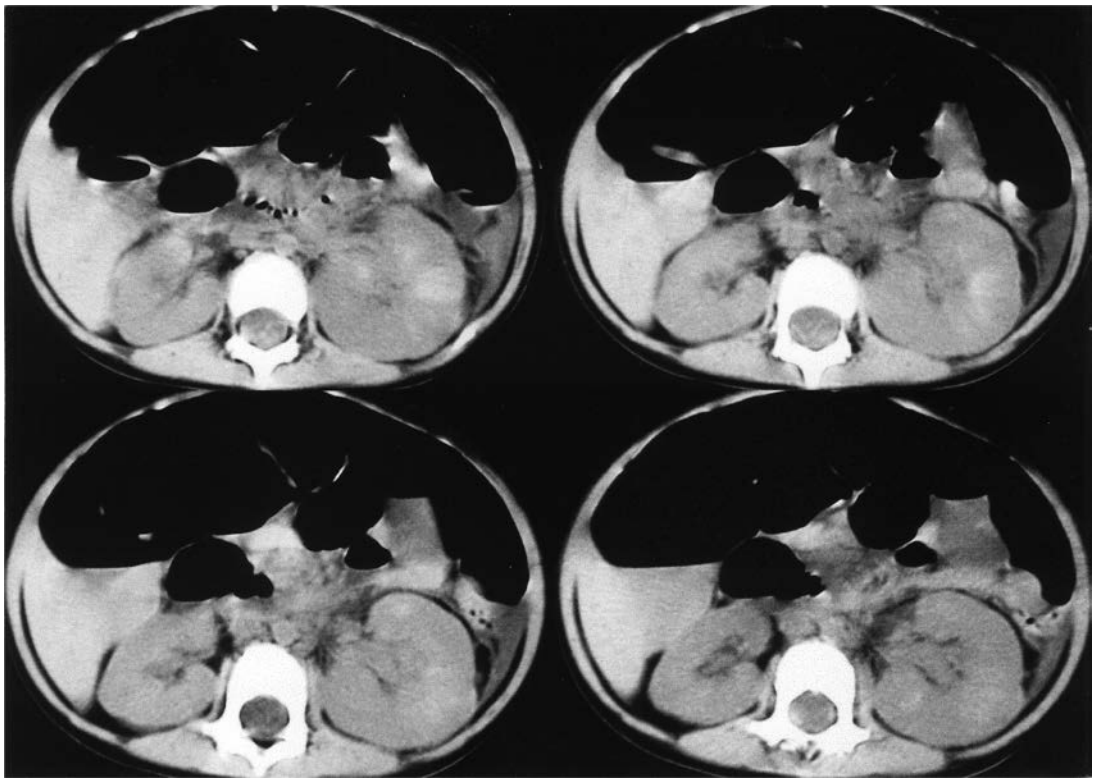

FIGURE 28.5 A 3-year-old girl with acute hemorrhagic pyelonephritis presenting with fever, gross hematuria, and *E. coli* bacteremia. Intravenous contrast material was not given for CT because of acute renal insufficiency requiring peritoneal dialysis. Non-enhanced CT shows that her left kidney is enlarged, with multiple slightly higher attenuation areas scattered throughout the parenchyma. Several similar, more subtle lesions are also present in the right kidney.

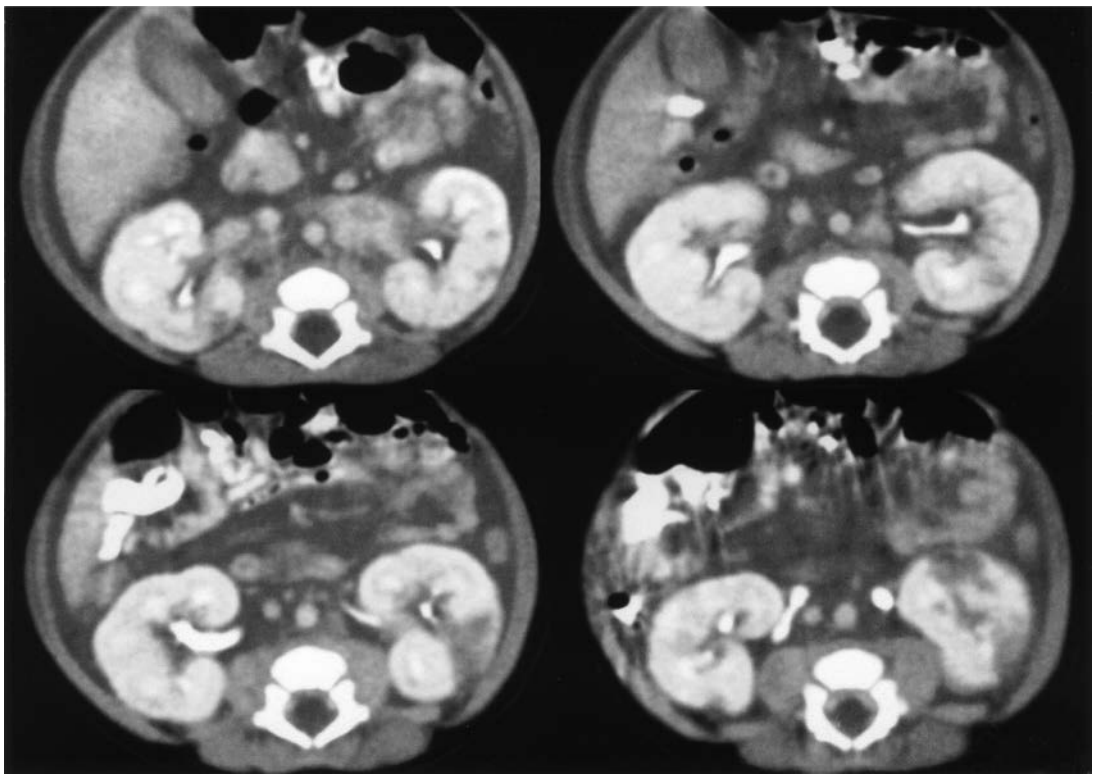

FIGURE 28.6 A 2-week-old boy with *Candida albicans* sepsis and bilateral fungal pyelonephritis. Contrast-enhanced CT shows both kidneys are enlarged and contain multiple scattered, peripheral, low-attenuation, non-enhancing parenchymal lesions.

Complications of Acute Pyelonephritis

Renal Abscess

Because of the nonspecific and often nondiagnostic images on US of a renal abscess, CT scan and MRI are often performed initially when renal abscess is suspected. For the most part, CT is the gold standard for imaging a renal abscess (Figure 28.7); however, the as low as reasonably achievable (ALARA) principle has caused a more modern trend toward the use of MRI. In addition, CT diagnosis is optimized by the use of iodinated contrasts, and these should not be used in children with renal failure or insufficiency, who seem to be the highest risk for renal abscess.[68] Most recently, some have prospectively evaluated the accuracy of the quantitative apparent diffusion coefficient (ADC) value obtained on DW MRI to differentiate nephritis from renal abscesses in patients with pyelonephritis.[69] They found that for the diagnosis of pyelonephritis, DW MRI had a higher sensitivity (95.3%) than non-contrast-enhanced CT (66.7%) and contrast-enhanced CT (88.1%). Areas of nephritis had significantly lower ADC values ($p < 0.001$) than the normal renal cortical parenchyma. In addition, renal abscesses had significantly lower ADC values ($p < 0.001$) than areas of nephritis. However, CT was more useful for the diagnosis of nephrocalcinosis and emphysematous pyelonephritis. Xanthogranulomatous pyelonephritis (XGP), perhaps the worst of all the complications of acute and chronic pyelonephritis, is characterized by granulomatous infiltration of the kidney by lipid-laden macrophages that leads to extensive parenchymal destruction.[41,58,70–73] It is usually caused by chronic *Escherichia coli* or *Proteus* sp. infection. There are nephrolithiasis and chronic obstruction in almost all cases. US appearance is nonspecific with a markedly enlarged echogenic kidney with abnormal architecture and almost no corticomedullary differentiation. In most cases, these findings, along with diffuse or focal hyperechoic calcifications or frank calculi, will alert the clinician, and further confirmation is usually obtained by contrast-enhanced CT scan. Because of the signature presence of calculi, MRI is of less value than CT in the imaging of XGP. On contrast-enhanced CT scan, the affected kidney is usually nonfunctioning and the parenchyma appears low in attenuation secondary to necrosis and extensive cellular infiltration of macrophages. Although rare, focal XGP is characterized by a large inflammatory irregular renal mass, often with extrarenal extension and a calcification or stone within the mass itself.

Pyonephrosis is an acute bacterial infection in an obstructed dilated collecting system that is best and most easily imaged by grayscale 2D US, and is characterized by usually severe hydroureteronephrosis filled with purulent urine. The debris is echogenic and layers dependently, as opposed to air bubbles, which if present will appear as similar brightly echogenic shadowing debris that will rise or float on top of the urine. Areas of focal or diffuse pyelonephritis often accompany pyonephrosis as well. If further imaging is needed, CT again has the advantage over MRI because it is often better at characterizing the presence of an obstructing calculus. Isolated debris in the collecting

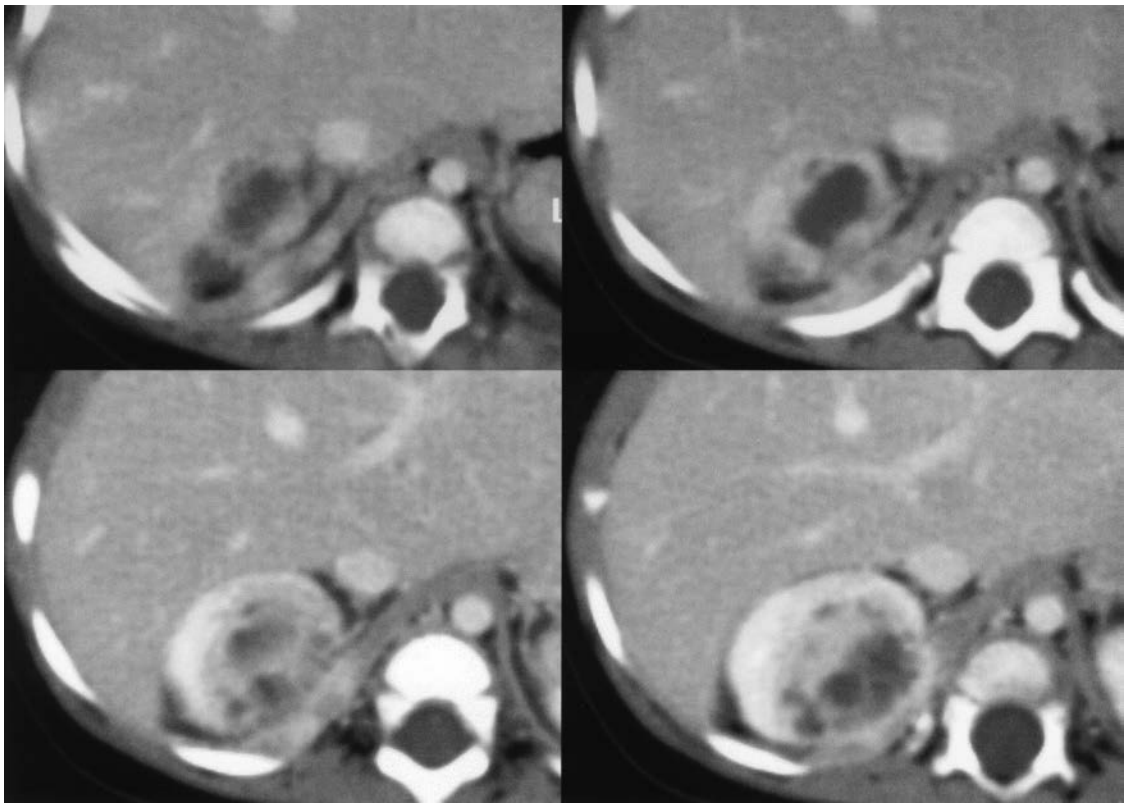

FIGURE 28.7 A 9-month-old boy with right acute pyelonephritis and intrarenal abscess. Contrast-enhanced CT shows a complex large-area abnormal enhancement with necrosis in the upper pole of the right kidney.

system is often seen with concentrated urine or can be seen early on with the endotoxin-induced atony of the collecting system in uncomplicated pyelonephritis. Similarly, air bubbles can be introduced into the bladder during routine or intermittent catheterization and, when present in the bladder, can get into the upper tract in children with VUR. These findings in isolation should not be mistaken for pyonephrosis.[41,58,65,74–76]

Renal scarring, or *chronic pyelonephritis*, otherwise known as reflux nephropathy, results from recurrent episodes of APN. Imaging of renal scars is largely performed in children by US. This modality has completely replaced IVP.[35–37,39,43,77] The US appearance of cortical scarring is heralded by cortical thinning or loss. Because of contraction and fibrosis, the adjacent calices are blunted. Cortical scars are more common at the poles due to the composite calices that allow for reflux into the medullary pyramids—so-called "intrarenal reflux"—and usually become more evident at least 3–6 months after acute infection, but can take up to 3 years to develop. Therefore, serial USs over time are important to follow linear measurements and document an acquired renal scar. Global scarring of the renal parenchyma is easily seen on US. The kidney is small with echogenic thin parenchyma. Focal scarring is likely more common, and much harder to see on US. The kidney may be normal size with imperceptible parenchymal volume loss. Cortical scars of this type are also more common in the polar regions of the kidneys. These should not be mistaken for fetal lobulations, which are uniformly spaced between pyramids and have no adjacent parenchymal thinning or blunting of calices. Chronic pyelonephritis is best seen by ^{99}mTc-DMSA renal cortical scintigraphy. Although DMSA is not good at differentiating a mature scar from congenital scars (i.e., dysplasia), there is a difference between an area of APN, an immature scar, and a mature scar. Mature scars are sharply defined wedge-shaped defects in the renal cortex, whereas a more acute or immature scar that has not had complete necrosis and fibrosis of the involved parenchyma will appear as a more irregular photopenic defect. Mature scars have renal volume loss with flattened renal contour due to complete fibrosis, whereas an immature or an acute defect will be more enlarged with an irregular, less defined renal outline.[43,45,51,78]

The role of MRI in the evaluation of renal abnormalities is increasing. MRI is useful in cases of compromised renal function and severe contrast allergy, and in children, with an emphasis on minimizing radiation exposure. Furthermore, MRI can be used as a problem-solving modality when the US findings are not diagnostic. Combined static–dynamic magnetic resonance urography (MRU) provides high-quality depiction of the urinary tract in infants and children, while allowing accurate determination of single-kidney function and reliable evaluation of urinary excretion.[63] In a comparison of MRU to DMSA scan for the identification of renal parenchyma defects in children with VUR, Cerwinka et al.[79] found that although DMSA scan and MRU were similar in their ability to diagnose parenchymal defects, MRU was considered to represent the true diagnosis in 11 of the 12 discordant cases in consensus review by four pediatric radiologists. MRU showed a much higher interobserver agreement with a weighted kappa of 0.96 for both kidneys. Based on their findings, they concluded that MRU was superior to DMSA scan in the identification of renal parenchyma defects. Likewise, in another study that used DMSA as the gold standard, Chan et al.[80] found that MRI with fat-saturated T1-weighted and after gadolinium, short tau inversion recovery (STIR) sequences was comparable to planar ^{99}mTc-DMSA. Static renal MRI using a fat-saturated T1-weighted sequence is a rapid, accurate, and minimally invasive technique for the detection of renal scarring that does not employ contrast enhancement or ionizing radiation.[60] By comparing the diagnostic performance of MRU in renal scar detection relative to that of the ^{99}mTc-DMSA scan in 49 children with UTI and VUR, Koçyiğit et al.[81] found that enhanced MRU is a robust technique for the morphologic assessment of the urinary system and detection of renal scars. The lack of radiation and contrast material makes this technique a much safer alternative to DMSA in children with VUR and a history of acute renal infection, particularly in those who require follow-up scanning and, consequently, considerable cumulative radiation exposure.

RENAL MASSES

At different ages, different types of masses are more common, and thus different imaging modalities are indicated. Due to its ease and ubiquitous nature, and the fact that in the neonate a palpable abdominal mass is more often cystic disease or is associated with hydronephrosis, US is the initial imaging modality of choice.[21,27,58] The most common solid renal mass in a neonate will be a congenital mesoblastic nephroma, and as the child gets older, Wilms' tumor (WT) would be the most common; therefore, a CT scan in these cases would most likely be the next imaging modality after an US finding of a solid mass. Certain genetic or familial syndromes carry an increased risk of developing WT, and frequent screening of the child is recommended with US. Although some authors question whether this changes the actual stage of the tumor at presentation if it should occur, most recommend screening renal US every 3 months until the age of 5 years in children with sporadic aniridia and WAGR association, and until the age of 8 years in children with hemihypertrophy, Drash syndrome, Perlman syndrome, and/or Beckwith–Wiedemann syndrome.[82,83]

RENAL TUMORS

When evaluating a solid renal tumor in a child, the goal should be to image the kidney to gain as much information as possible with a single imaging test, with as little radiation exposure as possible. As stated, this usually involves an US at the time of detecting a renal mass. Depending on the cell type and population, solid masses can be hypo-, iso-, or hyperechoic on US. Areas of hemorrhage, cystic degeneration, or necrosis will often appear irregular and hypoechoic. Given this variability, CT or MRI is the likely next step. All solid renal masses should be evaluated for size, laterality, intrarenal or extrarenal extension, focal

or diffuse pattern, cystic or mixed cystic–solid character, presence and pattern of calcification, perirenal or local adenopathy, vascular invasion or encasement, and neighboring organ involvement. The imaging test should also aide in staging and preoperative or neoadjuvant planning. It is also important to exclude any contralateral involvement or congenital renal anomaly that would reshape the treatment to a more renal-sparing plan. In most situations, all this information can be obtained with a single CT or MRI study,[84] but in atypical cases or cases where vascular invasion cannot be excluded, additional imaging is needed.

Wilms' Tumor

WT is the most common solid renal malignancy in childhood and accounts for 5% of all childhood malignancies. Most WTs are solitary, large, and confined to the kidney and of favorable histology. Favorable histology is present in ~90% of WTs.[85–91] Therefore, for the most part, the stage of the tumor is the most important prognostic factor. Anaplastic or unfavorable histologic variants have a much poorer prognosis. As long as they are completely resected at surgery without tumor spill, a tumor that is confined to the kidney (stage I) or an extrarenal tumor, even with lymph node or inferior vena cava involvement (stage II), has a >98% survival with favorable histology and a >80% survival if an unfavorable histology. If there is tumor spill at surgery or an incomplete resection (stage III), survival drops to 94% for favorable histology and 72% for unfavorable histology.[92] Staging and assessment of WT is usually performed with contrast-enhanced CT scan. On precontrast CT scan, the tumor appears heterogeneous and often large (~10 cm average).[58,93] On contrast-enhanced CT scan, the tumor is often heterogeneous as well, with enhancement of viable tumor and lack of enhancement of areas of cystic degeneration and necrosis. Although most tumors are encased in a pseudocapsule of compressed surrounding parenchyma, extrarenal invasion or displacement of surrounding bowel and vasculature can be seen. Synchronous bilateral Wilms' tumor (BWT) occurs in 4%–8% (Figure 28.8). However, approximately 1% of children with unilateral WT develop contralateral disease. Coppes et al.[94] assessed the demographic and histologic features associated with metachronous BWT. Although surveillance for metachronous lesions was recommended for those children with nephrogenic rests (NRs) who are diagnosed after the age of 12 months, children younger than 12 months diagnosed with WT who also have NRs, in particular perilobar NRs, have a markedly increased risk of developing contralateral disease and require frequent and regular surveillance for several years. Although contralateral exploration is still an acceptable practice in equivocal cases, modern CT and MRI have led to a more accurate definition of intrarenal pathology. In a study designed to answer the question of whether contralateral kidney exploration is still necessary in patients with unilateral WT, Kessler et al.[95] found that in all patients, preoperative radiological investigation was accurate in excluding bilaterality. With modern imaging techniques and effective chemotherapy, extensive contralateral renal exploration may no longer be mandatory for managing WT. Ritchey et al.[96] evaluated the incidence and outcome of missed bilateral lesions. In this study, there were 188 patients with BWT, or 5.6% of the total 3335 registered. CT was performed in all patients. After subsequent management of missed lesions and a median follow-up of 9 years, there were no recurrences in any kidney with a missed lesion, and all patients were alive and disease-free at last follow-up. From these studies, it seems that omission of routine exploration will not likely affect the outcome or management of newly diagnosed WT provided preoperative CT or MRI is performed.

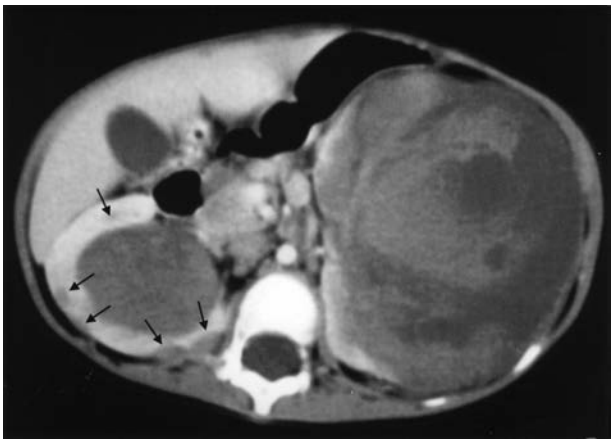

FIGURE 28.8 A 3-year-old girl with bilateral synchronous Wilms' tumors and right nephroblastomatosis. At contrast-enhanced CT, the left kidney is almost entirely replaced by a large, partially necrotic mass (Wilms' tumor) and there is a somewhat smaller mass (Wilms' tumor) distending the right renal sinus. Numerous tiny, low-attenuation perilobar nephrogenic rests (arrows) are visible in the residual enhancing right kidney.

WT staging has to include imaging of at least the entire abdomen and chest since lung is the most common presentation of metastatic disease. For the most part, CT is used most often for staging because it is the most ubiquitous, and does not suffer as much as MRI from motion artifact, which demands anesthesia with all the inherent risks. Depending on final tumor histology, a bone scan and brain MRI scan must be performed as well in the case of clear cell sarcoma and rhabdoid tumor of the kidney, although these are not strictly categorized as WTs any longer. MRI is specifically recommended and often needed, independent of CT scan, in cases where there is suspected vena cava or right atrium tumor thrombus (Figure 28.9), infiltration of the liver and/or diaphragm, or continuous tumor extension into the chest cavity. MRI is superior to CT scan in these situations because postscan software and computer-aided techniques can better differentiate neighboring tissues by either their patterns of gadolinium enhancement, different diffusion coefficients, differing fat suppression properties, or appearance on T1- and T2-weighted images.[62] In the case of screening or for postoperative surveillance, US is the procedure of choice because these are undoubtedly serial examinations over long periods of time, and the inherent anesthesia associated with MRI or radiation exposure with CT scan is an unacceptable risk to the growing child.

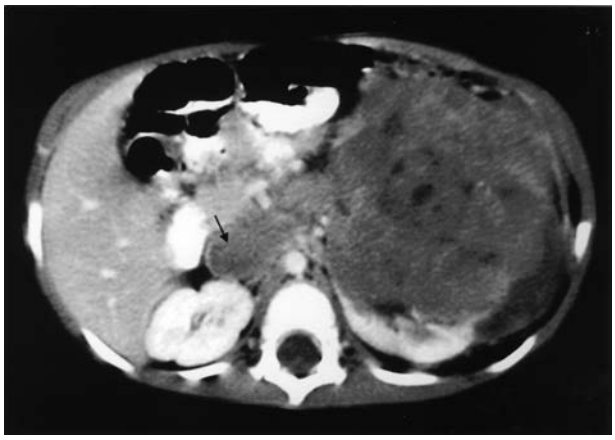

FIGURE 28.9 A 2-year-old girl with large left Wilms' tumor with extension into the left renal vein and inferior vena cava. Contrast-enhanced CT shows a large non-enhancing, solid left renal mass containing multiple small areas of necrosis and hemorrhage. Low-attenuation soft tissue is visible distending the left renal vein and inferior vena cava (arrow).

Nephroblastomatosis

Nephroblastomatosis is when there is nephrogenic blastema that persists in the kidney that can undergo malignant transformation into a WT postnatally. These nephrogenic rests, as they are called, can be either perilobar, intralobar, or very rarely panlobar. The perilobar are much more common (Figure 28.8), while the less common intralobar will more commonly undergo malignant transformation. Although some nephrogenic rests are not macroscopic, most can be seen on US or CT scan, with the majority being identified with a combination of imaging studies, although CT is more sensitive than US. Nephrogenic rests characteristically do *not* enhance with contrast on either CT or MRI (Figure 28.10). They appear as low-attenuation areas on CT. On T1- and T2-weighted MRI, they appear hypointense compared with the normal renal cortex and isointense compared with the renal medulla.[94] Children with nephrogenic rests that are identified on imaging, and those children that have syndromes and conditions that are known to have a high incidence of nephrogenic rests, should have serial renal imaging at least every 3–6 months during infancy and early childhood.[87,89,93] This interval can be increased as the children get older.[58,93,97] The best modality for surveillance of this type is US. Each study should be compared with the previous studies, looking not only for changes in the echotexture of areas of suspicion but also for new suspicious areas, as well as focal or asymmetric enlargement, or changes in the renal contour or outline. Some have suggested power Doppler US to increase the sensitivity for detecting smaller renal masses not seen on routine 2D US. Regardless, any suspicious areas or changes should be followed immediately by contrast-enhanced CT or MRI.

FIGURE 28.10 A 14-month-old boy with panlobar nephroblastomatosis, presenting with a markedly distended abdomen and bilateral palpable flank masses. Contrast-enhanced CT shows the kidneys are almost completely replaced by multiple low-attenuation, non-enhancing, solid masses. Residual compressed strands of functioning renal parenchyma are visible between the masses.

Neuroblastoma

Neuroblastoma (NB) is an adrenal tumor or a tumor of neuroectodermal tissue origin that is separate from the kidney and can arise anywhere along the sympathetic chain. The most common site of origin is in the retroperitoneum. NB is the most common extracranial solid tumor in children, with 90% of them diagnosed before the age of 5 years. It is worth mentioning in this context because 20% of NBs involve the kidney, and oftentimes they cannot be distinguished from WT on routine US and CT images. Both WT and NB are heterogeneous solid masses with mixed areas of cystic degeneration, necrosis, and hemorrhage on CT scan. NB characteristically has a low signal intensity on T1-weighted and high signal intensity on T2-weighted magnetic resonance images. Several imaging clues can distinguish WT from NB. WT arises from within the kidney, while NB arises from the adrenal or retroperitoneum, and therefore will appear to displace the kidney. NB also often lacks a well-defined capsule, whereas WT has a well-defined pseudocapsule of compressed renal parenchyma. WT can invade major renal vessels, whereas NB engulfs major renal vessels, causing compression and clinical hypertension. More than 90% of NBs have calcifications in the tumor, whereas only about 15% of WTs have calcifications. WT most commonly metastasizes to the lungs, whereas NB will metastasize to cortical bone, bone marrow, the liver, and the orbit. Generally, children with NB are often very ill with systemic symptoms such as weight loss, anorexia, and malaise since ~65% present with metastatic disease. There is no absolute best imaging modality for NB, but MRI has emerged over the years to have several advantages over CT, besides the lack of radiation exposure. MRI is excellent at examining the relationship of a mass to surrounding tissues of different water diffusion properties. In addition, often MRI can detect metastases to bone marrow of the extremities in young children and vertebrae in older children. NB can spontaneously regress in infancy (stage IV), making it difficult to distinguish from the more common adrenal hemorrhage, which also presents as a solid and/or cystic adrenal mass. NBs that occur in infancy can be distinguished from adrenal

hemorrhage because the former will have elevated urinary catecholamine. Between 85% and 95% of children with NBs excrete catecholamine or their metabolites in the urine.[98]

Clear Cell Sarcoma

Clear cell sarcoma of the kidney (CCSK) was once considered a variant of WT, and it is reported by the National Wilms Tumor Study Group (NWTSG) to account for 4% of pediatric renal tumors.[99] CCSK tends to manifest with an average age at presentation of 2–3 years, and exhibits a male predominance. CCSK yields a much poorer prognosis than WT, with current long-term survival rates of 60%–70%.[100] CCSK is often misdiagnosed given the infrequency with which it is clinically encountered. The morphological diversity and the lack of specific diagnostic markers also contribute to the high rate of misdiagnosis.[101] Approximately 5% of patients will have metastatic disease at diagnosis. There is a 40%–60% incidence of skeletal metastasis present among patients with CCSK.[102] Additionally, CCSK has been reported to metastasize to unusual sites, such as the scalp, epidural space, nasopharynx, neck, paraspinal area, abdominal wall, axilla, and orbit.[103] Imaging characteristics are usually indistinguishable from WT. US shows heterogeneous echogenicity with cystic components and necrosis. Large fluid-filled cystic spaces with echogenic septa may also be present.[104] CT will reveal inhomogeneous enhancement, with attenuation less than that of normal renal parenchyma. Furthermore, these tumors also contain areas of low attenuation corresponding to necrosis and cysts.[104] Skeletal metastasis tends to be osteolytic in nature, but osteoblastic metastasis also occurs; therefore, both hot and cold defects can be seen on bone scan.[105]

Malignant Rhabdoid Tumor

Although renal malignant rhabdoid tumor was historically included in earlier treatment protocols of the NWTSG, this tumor is now recognized as an entity separate from a WT. In contrast to a WT, a malignant rhabdoid tumor of the kidney is characterized by the early onset of local and distant metastases and resistance to chemotherapy. Whereas the overall survival rate for WTs exceeds 85%, the survival rate for renal malignant rhabdoid tumors is only 20%–25%. Malignant rhabdoid generally presents during the first year of life.[106] Malignant rhabdoid tumor is associated in up to 50% of patients with a histopathologically diverse group of primary central nervous system tumors that include primitive neuroectodermal tumor, ependymoma, and astrocytoma.[107] This group of primary central nervous system tumors can be present when the renal mass is detected, or they may appear later in the disease process. CT, US, and MRI will reveal a large, aggressive, infiltrating, solid renal mass. The mass will often arise centrally, adjacent to the renal hilum, and invade and compress surrounding parenchyma as the mass enlarges. Linear calcifications are common, and may appear to outline distinct tumor lobules. Rapid enlargement of the mass may lead to necrosis and hemorrhage. Peritumor hemorrhage may also occur, and this may lead to characteristic crescent-shaped fluid collections at the periphery of the mass. Given the frequent association of both primary and metastatic central nervous tumors, CT or MRI of the brain should be performed whenever the diagnosis of malignant rhabdoid tumor is suspected.

Renal Cell Carcinoma

Pediatric renal cell carcinomas account for approximately 2% of all new pediatric renal tumors.[108] The most common subtypes seen preferentially in children are the translocation-associated tumors, papillary renal cell carcinoma, renal medullary carcinoma, and oncocytic renal cell carcinoma following NB.[109] The mean age at presentation is 11–12 years old, and it has been reported as early as 6 months of age. Patients commonly present with painless gross hematuria, abdominal pain, or a palpable mass. The imaging features of renal cell carcinoma in children are similar to those found in renal cell carcinoma in adults. The tumor usually appears hyperechoic on US and hyperdense on CT with heterogeneous contrast enhancement (Figure 28.11).[110,111] Necrosis and hemorrhage are common, and calcification is more common than in WT. There is a relatively good prognosis if the entire lesion can be removed surgically. If the lesion is incompletely resected or there is distant metastasis present, the prognosis is poor.[112]

Renal Medullary Carcinoma

Renal medullary carcinoma is a very aggressive malignant neoplasm that occurs almost exclusively in children and young adults with sickle cell trait or sickle cell disease.[113] These patients usually present with hematuria, flank pain, weight loss, fever, and abdominal pain. US and a CT scan usually show an infiltrative and distinct intrarenal mass that frequently arises from the central region of the kidney and commonly invades the renal sinus fat.[113–115] MRI and CT both demonstrate heterogeneous enhancement. Renal medullary carcinoma arises along the urothelial margin of the renal medulla and grows quickly into the renal pelvis, leading to early vascular and lymphatic invasion. Peripheral satellites in the renal cortex and pelvic soft tissue, as well as venous and lymphatic invasion, are usually present. Common sites of metastasis include the contralateral kidney, liver, lungs, and lymph nodes.

Leukemia, Lymphoma, and Lymphoproliferative Diseases

Histologic evidence of renal infiltration is common on postmortem examination of children who die from leukemia or lymphoma. Clinical and radiographic evidence of renal involvement is much less common during life.[116–118] Clinical signs of renal involvement, including palpable mass, hematuria, or reduced renal function, rarely precede other manifestations of the disease. Renal involvement is usually detected during staging or follow-up imaging studies in patients with known disease elsewhere.

Renal involvement is usually bilateral in both leukemia and lymphoma.[117,118] Leukemic infiltration of both kidneys

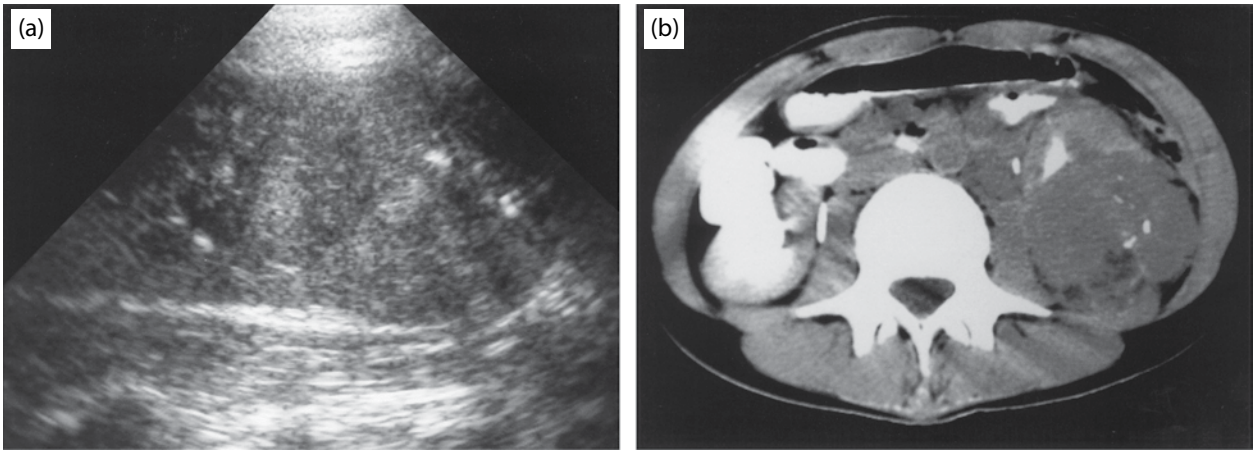

FIGURE 28.11 A 13-year-old girl with renal cell carcinoma of the lower pole of her left kidney, presenting with abdominal pain and a palpable left abdominal mass. (a) Ultrasound: longitudinal view of the left kidney shows a large, solid, slightly heterogeneous lower pole mass. Multiple small calcifications are visible within the mass. (b) Contrast-enhanced CT through the kidneys shows a large, solid mass in the lower pole of the left kidney posteriorly. Small calcifications are present within the mass. The residual functioning portion of the left kidney is visible anteriorly.

causes diffuse renal enlargement with disruption of the normal corticomedullary architecture (Figure 28.12). A discrete mass is less common in leukemia than in lymphoma. In lymphoma, neoplastic infiltration of the renal interstitium initially also causes nonspecific renal enlargement, with a diffuse increase in the parenchymal echogenicity on US. As the infiltrating neoplastic cells coalesce to form larger, hypoechoic masses, the kidney enlarges and loses its reniform shape. The renal architecture is increasingly disrupted, and the parenchyma becomes diffusely more inhomogeneous. At postcontrast CT, multiple coalescing low-attenuation, nonenhancing, solid masses are visible (Figure 28.13).[116–118] Perinephric extension and renal hilum and retroperitoneal lymph node involvement is better demonstrated at CT or MRI than at US. Follow-up imaging after successful treatment and regression of the masses often shows extensive cortical defects that can be indistinguishable from other causes of renal atrophy and cortical scarring. Dystrophic parenchymal calcifications are also occasionally seen following treatment for some forms of renal lymphoma (Figure 28.14).[119]

Lymphoproliferative disorders are an important consideration in patients who have severely impaired T-lymphocyte-mediated immunity, and are potentially life-threatening conditions. Lymphoproliferative disorders have been reported as a complication of immunosuppression for organ transplantation,[120–122] in primary immunodeficiency, and in acquired immunodeficiency syndrome (AIDS). Regardless of the immune defect, Epstein–Barr virus is critical in mediating the induction of polyclonal B-lymphocyte proliferation that leads to the development of lymphadenopathy, focal parenchymal masses, and diffuse infiltration of solid organs.[121,123] Involvement can be focal, multifocal, or widely disseminated. Any organ or body space can be involved. The gastrointestinal tract, solid abdominal organs, and abdominal lymph nodes are most often affected. Renal involvement occurs in 17%–20% of cases and has imaging features similar to those of leukemia and lymphoma.

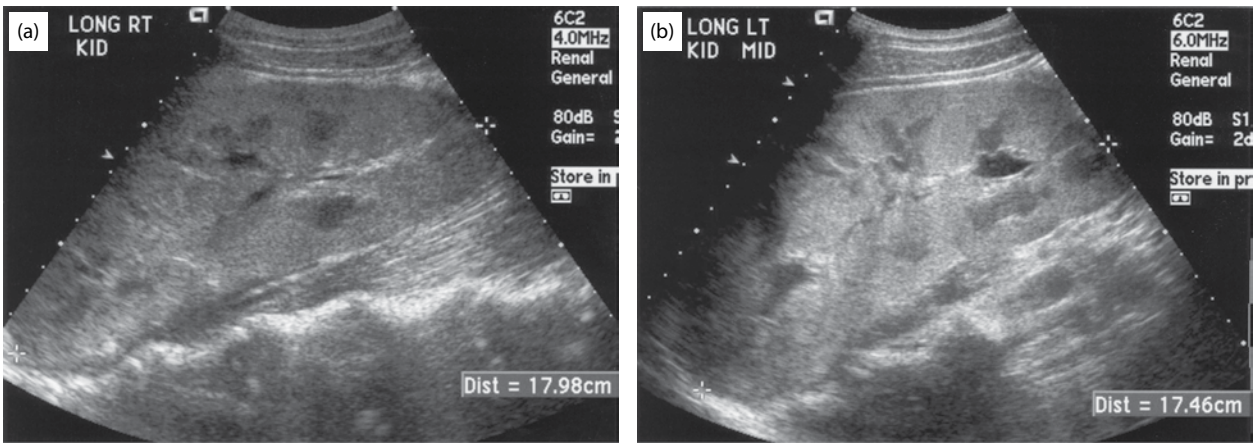

FIGURE 28.12 An 18-year-old boy with relapsed acute lymphocytic leukemia and diffuse bilateral leukemic renal infiltration. Ultrasound shows markedly enlarged, echogenic kidneys with multiple small, relatively hypoechoic, solid masses scattered throughout the parenchyma bilaterally. (a) Ultrasound: longitudinal view of the right kidney (length 18.0 cm). (b) Ultrasound: longitudinal view of the left kidney (length 17.5 cm).

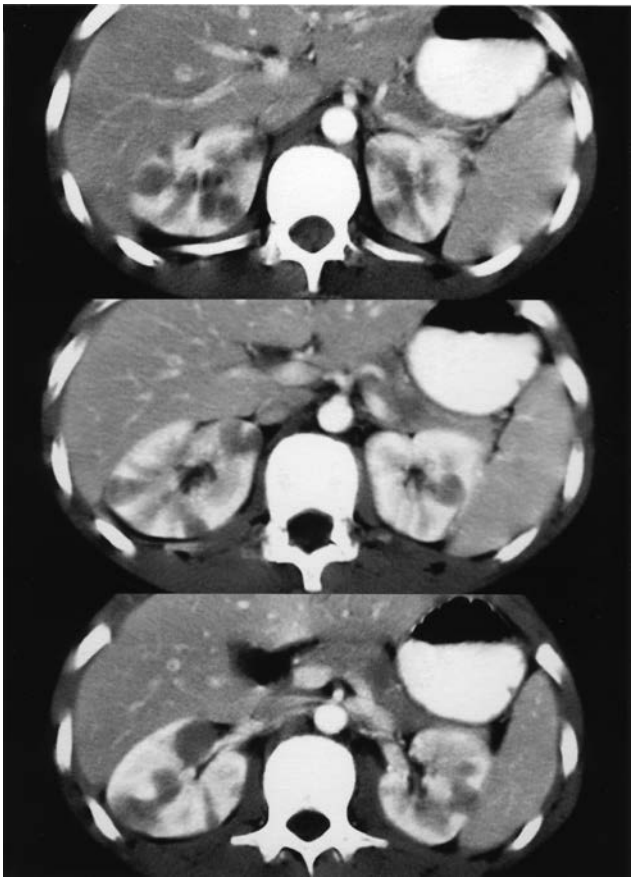

FIGURE 28.13 A 14-year-old boy with Burkitt's lymphoma of both kidneys. Contrast-enhanced CT shows multiple nonsegmental, low-attenuation, non-enhancing solid masses scattered randomly throughout both kidneys.

Congenital Mesoblastic Nephroma (Fetal Renal Hamartoma)

Congenital mesoblastic nephroma (congenital fetal renal hamartoma) is the most common primary, renal tumor in the newborn, and it occurs almost exclusively in the first year of life.[124–127] Once thought of as a congenital form of WT, mesoblastic nephroma is distinguished by its younger presentation, characteristically nonaggressive course, limited growth potential, predominantly mesenchymal derivation, and lack of malignant epithelium. Recurrence is rare as long as the entire mass is removed, although metastatic spread to the lungs and brain has been reported.[128] A palpable mass is generally present at diagnosis. However, mesoblastic nephroma is increasingly being detected at prenatal US. On US, mesoblastic nephroma appears as a large solid renal mass. The mass can appear either homogeneous or complex. Cysts are present in up to 60% of cases, and small, scattered calcifications can also occasionally be visible.[129] On CT, the tumor presents as a nonenhancing, low-attenuation mass surrounded by enhancing residual normal parenchyma (Figure 28.15). Cystic areas of necrosis and hemorrhage are readily demonstrated on CT, as well as calcifications, when they occur.[125,126]

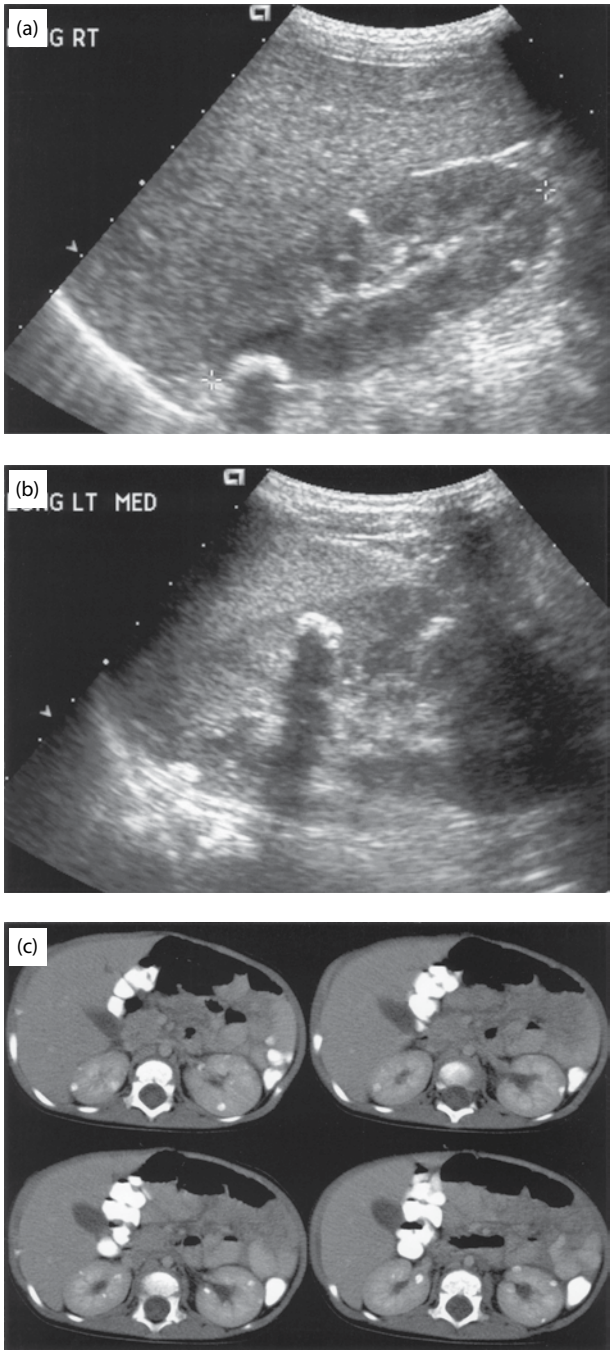

FIGURE 28.14 A young boy with bilateral dystrophic renal parenchymal calcifications 3 months after treatment for acute myelogenous leukemia. (a) Ultrasound: longitudinal view of the right kidney. (b) Ultrasound: longitudinal view of the left kidney. (c) Contrast-enhanced CT: four axial images through the kidneys.

Multilocular Cystic Nephroma

Multilocular cystic nephroma is a benign, cystic renal tumor that is made up of noncommunicating cysts of differing sizes that are separated by thin septa. These septa are composed of fibrous tissue, tubular elements, and immature blastema.[130–132] The tumor can be localized to one part of the kidney or involve the entire kidney. Rarely,

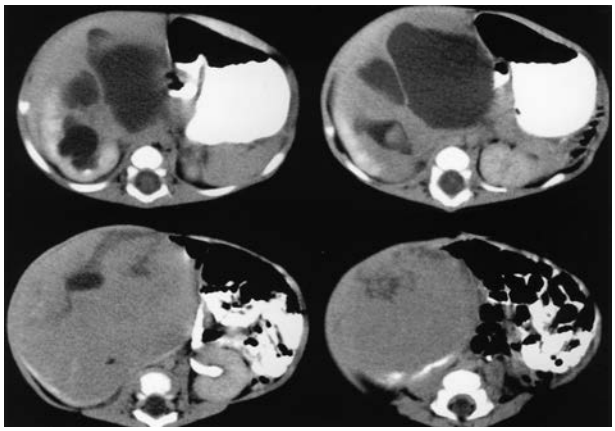

FIGURE 28.15 An 8-week-old girl with right congenital mesoblastic nephroma, presenting with a palpable right abdominal mass. Contrast-enhanced CT shows a large, solid, non-enhancing right renal mass that compresses the renal pelvis, resulting in obstruction and severe hydronephrosis.

multiple discrete lesions are present. Although the cyst walls occasionally contain cellular elements that are histologically similar to WT, multilocular cystic nephroma has no real malignant potential and local recurrence is rare following complete resection. The imaging features of multilocular cystic nephroma are distinctive.[130,131] The tumor appears as a complex, multicystic mass with uniformly thin septa separating the cysts. The septa are usually more conspicuous on US than on CT, although they can enhance somewhat after administration of contrast material. Thicker septa and septa that appear irregular or nodular are unusual in multilocular cystic nephroma, and this finding should raise concern that the lesion might instead represent a cystic WT.[132] Septal calcifications are occasionally present in adults, but are rarely seen in children. On MRI, the tumor capsule and septa appear hypointense on both T1- and T2-weighted images, with minimal enhancement after gadolinium.[133] The signal intensity of the fluid within the locules depends on their hemorrhagic and proteinaceous composition.

Angiomyolipoma

Angiomyolipoma is a benign, nonencapsulated tumor of the kidney composed of blood vessels, smooth muscle, and fat.[134–136] In the pediatric population, angiomyolipoma is highly suggestive of the diagnosis of tuberous sclerosis, and is usually multiple and bilateral (Figure 28.16). Other clinical and imaging features of tuberous sclerosis are usually present. Far less often, angiomyolipomas are diagnosed in a child with undiagnosed tuberous sclerosis who presents with a palpable mass or hematuria. Renal cysts also occur in patients with tuberous sclerosis (Figure 28.17) and can coexist with angiomyolipomas.[135–137] Visualization of fat within a renal mass in a child is highly suggestive of the diagnosis of angiomyolipoma.[134–136] Rarely, the tumor has more vascular and muscular components and contains little or no visible fat. Calcification is usually absent. Angiomyolipomas are usually very echogenic on US and have very low attenuation, similar to perinephric fat on nonenhanced CT scans. On MRI, the tumors are hyperintense on both T1- and T2-weighted images. Because angiomyolipomas are extremely vascular, they enhance very intensely on both CT and MRI. Larger angiomyolipomas tend to bleed, resulting in intratumoral, subcapsular, and perinephric hemorrhage.

Renal Lymphangioma and Lymphangiomatosis

Renal lymphangioma is a rare, benign, cystic renal neoplasm with imaging features similar to those of multilocular cystic nephroma.[138,139] Renal lymphangioma is either unilocular or multilocular in nature and is usually solitary, although multiple lymphangiomas do occur. Renal lymphangiomatosis is an extremely rare disorder that is characterized by massive bilateral nephromegaly. There are residual islands of functional renal parenchyma appearing as irregular bands separating the innumerable cysts, which may simulate the appearance of advanced autosomal dominant polycystic kidney disease or tuberous sclerosis.[140] Lymphangiomatosis can be limited to the kidneys, or it can

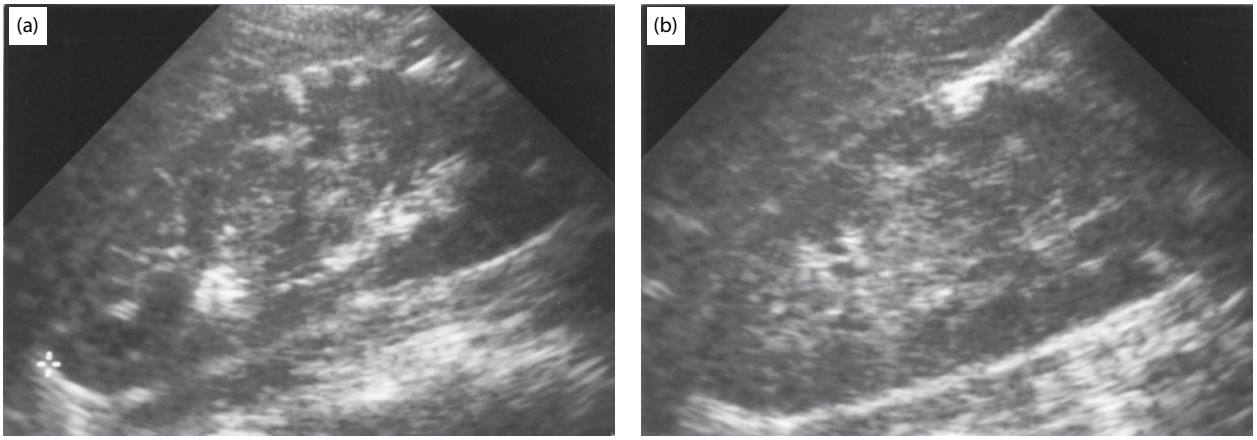

FIGURE 28.16 A 4-year-old girl with tuberous sclerosis and bilateral renal angiomyolipomas. Ultrasound shows multiple small, solid, non-shadowing echogenic masses scattered throughout both kidneys. (a) Ultrasound: longitudinal view of the right kidney (length 7.8 cm). (b) Ultrasound: longitudinal view of the left kidney (length 7.9 cm).

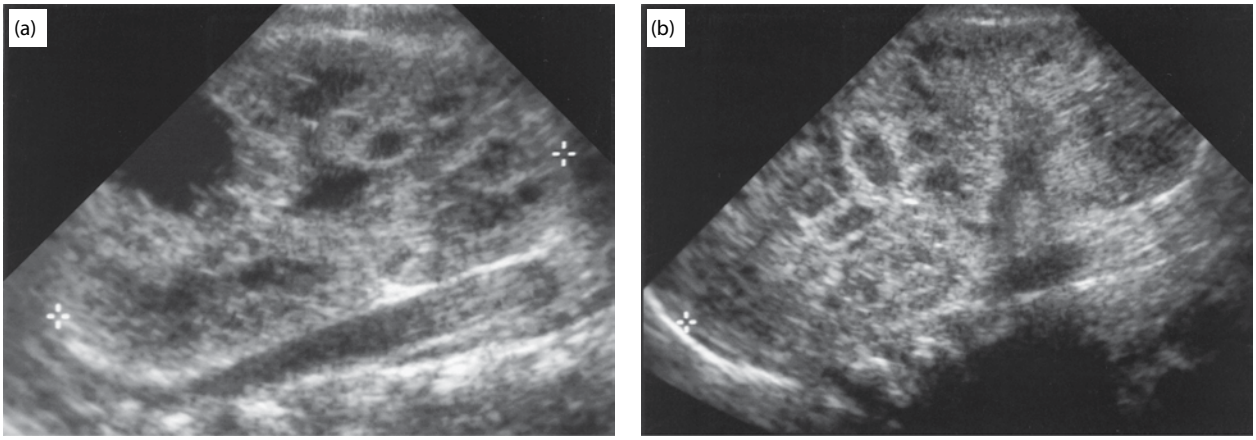

FIGURE 28.17 A 3-week-old boy with tuberous sclerosis and polycystic kidney disease. The kidneys are both enlarged and heterogeneous with numerous irregular cysts bilaterally. (a) Ultrasound: longitudinal view of the right kidney (length 7.0 cm). (b) Ultrasound: longitudinal view of the left kidney (length 7.9 cm).

occur in association with more extensive retroperitoneal involvement. Cystic pulmonary lesion may also occur.[141]

RENAL VASCULAR DISEASE

Renal Vein Thrombosis

Renal vein thrombosis (RVT) in children presents most commonly with gross hematuria, hypertension, and an enlarged, palpable kidney.[21,27,58,142,143] The greatest risk occurs in premature infants, infants of diabetic mothers, neonates and infants with severe dehydration, and infants with hypotension, sepsis, or asphyxia. Children with coagulopathy are also at higher risk of RVT. RVT is usually unilateral, and the affected kidney usually functions poorly. Bilateral thrombosis is rare, but when it occurs, it causes severe renal insufficiency.[144] In neonates and infants, thrombus formation begins in the smaller intrarenal veins, while the main renal vein and inferior vena cava often remain patent. In neonates with adrenal hemorrhage, extension of thrombus into the kidney from the adrenal vein can lead to ipsilateral RVT. This is more commonly on the left, since the left adrenal vein drains directly into the left renal vein.

RVT is usually diagnosed by US.[21,27,58,145–149] In the acute phase, the kidney appears globally enlarged, and the parenchyma is diffusely echogenic with loss of corticomedullary differentiation. Larger thrombi within interlobar and intralobar renal veins appear as linear, echogenic bands radiating peripherally between the renal lobes. Although in some cases thrombus can also be seen extending into the main renal vein and inferior vena cava, the main renal vein may be patent. One indication of extension into the main renal vein that is still patent may be reduced flow amplitude on Doppler US. More importantly, renal artery Doppler US may show reduced or even retrograde flow during diastole, with a markedly increased resistive index.[34] On mercaptoacetyltriglycine (MAG3) renal scintigraphy, the kidney is globally enlarged, with markedly reduced or absent uptake, as well as no excretion of radiotracer. During recovery after hydrolysis, for example, the affected kidney decreases in size as the edema recedes. Restoration of flow and function is variable. Serial USs are required to document renal size stabilization and resumption of normal growth rate. Persistent cortical hyperechogenicity and diminished corticomedullary differentiation indicate parenchymal atrophy and are associated with poor functional recovery. With severe parenchymal infarction and parenchymal necrosis, severe atrophy and cyst formation can result in a small echogenic, poorly functioning kidney.[21,22,27,58,145,146] In the chronic phase, punctate, linear, or branching calcification can appear within the thrombus in the intrarenal veins.[150,151] The presence of linear and punctate renal calcification in a neonate with a small echogenic kidney is strongly suggestive of prenatal RVT.[152]

CT and MRI are rarely performed in children with RVT, since the diagnosis is readily established on US and MAG3 renal scintigraphy.[58,142,147] However, when used, CT and MRI typically show that the affected kidney is enlarged and edematous during the acute phase. Perfusion is diminished with heterogeneous parenchymal attenuation and markedly reduced or no contrast enhancement. Parenchymal infarction and hemorrhage are common, and easily seen on CT and MRI. Associated adrenal hemorrhage and thrombosis of the inferior vena cava are also readily visualized. In the chronic phase, parenchymal atrophy ensues, with calcification of the residual thrombus in the renal rein and inferior vena cava.[148,149,153]

Renal Artery Thrombosis

Nontraumatic renal artery thrombosis can occur primarily following umbilical or femoral artery catheterization, in infants of diabetic mothers, and in infants and children with sepsis, severe dehydration, coagulopathy, or vasculitis.[154] The extent of parenchymal injury depends on the size of the occluded vessel. Complete occlusion of the main renal artery results in global renal infarction.[27,155,156] During the acute phase, the kidney may initially remain normal in size or even be slightly small, and the cortex becomes hyperechoic, although the pyramids remain hypoechoic. Doppler US is the diagnostic imaging of choice, and characteristically shows reduced or absent flow

in the main and segmental renal arteries with a normal or low resistive index.[154] Visualization of the echogenic intraluminal filling defect representing the thrombus within the main renal artery is diagnostic. As parenchymal infarction and hemorrhage develop, the kidney swells and becomes increasingly echogenic and heterogeneous, ultimately leading to complete disruption of the normal corticomedullary architecture. Functional evaluations, such as renal scintigraphy, show no uptake or excretion on the affected kidney. As in RVT, CT and MRI are rarely performed in neonates and infants with renal artery thrombosis.[154] The anatomic and functional outcomes depend on the extent of parenchymal infarction and the timing and degree of revascularization. Chronic ischemia results in an atrophic and a poorly or nonfunctioning echogenic kidney that is small with smooth, reniform contours. Small parenchymal calcifications and cysts can also be seen. Segmental renal artery occlusion causes a wedge-shaped, avascular segmental defect with its apex at the renal hilum and its bases at the renal capsule.[27,156] Doppler imaging can confirm the absence of flow in the infarcted area, although scar formation can be difficult to differentiate from that seen in chronic pyelonephritis. Intravascular sonographic contrast agents may improve visualization of cortical perfusion defects with power Doppler US.[157,158]

Hemolytic Uremic Syndrome

Hemolytic uremic syndrome is a bacterial toxin-mediated vasculitis that is manifested clinically by acute renal failure, microangiopathic hemolytic anemia, fever, and thrombocytopenia. The disease primarily affects children of <5 years of age and is frequently preceded by an episode of gastroenteritis associated with severe abdominal cramping and bloody diarrhea. Initial inflammation with thrombosis of small intrarenal arteries and capillaries leads to acute renal failure with severe oliguria or anuria and hypertension. Spontaneous recovery usually occurs within 3–4 weeks, although dialysis is often necessary during the acute phase.[159,160]

During the acute phase, the kidneys are normal in size or slightly enlarged, as in renal artery thrombosis. The renal cortex is diffusely hyperechoic and the medullary pyramids are hypoechoic.[27,161,162] The resistive index is elevated on Doppler US with markedly reduced or absent forward diastolic flow in the renal arteries. Occasionally, flow can even be reversed during diastole, as in RVT. Normalization of the arterial waveform may precede the onset of diuresis during the recovery phase.[76] Cortical echogenicity also returns to normal in most children who experience complete recovery of renal function.[163,164]

Nephrocalcinosis and Other Causes of Renal Medullary Hyperechogenicity

Medullary nephrocalcinosis is the most common cause of renal medullary hyperechogenicity in infants and children.[27,58,165–167] Hypercalciuria, increased urinary phosphate excretion, and hypercalcemia are important predisposing factors. Dystrophic renal calcification can also form secondary to severe parenchymal injury from trauma, infection, or infarction. US is the optimal imaging method for the detection and monitoring of nephrocalcinosis, which shows a characteristic periphery-to-center progression, with increased echogenicity first developing along the margins of pyramids (Figure 28.18).[27,58,168–171] Over time, this peripheral echogenic rim gradually thickens, eventually filling in the centers of the pyramids. In the most severe cases, the pyramids are diffusely, intensely echogenic with posterior acoustic shadowing. Aggregates of extracellular calcium near the papillary tips (Randall's plaques) can perforate the caliceal epithelium, leading to extrusion of calculi into the collecting system (Anderson–Randall–Carr phenomenon). Even in cases with marked medullary hyperechogenicity on US and increased medullary attenuation on nonenhanced CT, the calcification is not always visible on abdominal radiographs. Cortical calcification usually occurs only in the presence of advanced medullary nephrocalcinosis and is associated with marked hypercalcemia or severe generalized parenchymal injury, or both. Cortical nephrocalcinosis manifested on sonogram by a generalized increase in cortical echogenicity, cortical acoustic shadowing, loss of corticomedullary differentiation, and atrophy. Renal medullary hyperechogenicity is also seen in a number of uncommon lysosome storage diseases, including glycogen storage disease, Lesch–Nyhan syndrome, and Wilson's disease.[165,166,172–174] Both hypercalciuria and microscopic evidence of increased medullary calcium deposition have been reported in patients with these disorders.[171] Hyperuricemia might also contribute in some patients, as it is known to produce hyperechoic pyramids in adults with gout and in children with leukemia. In some subtypes of glycogen storage disease, the kidneys are enlarged and become increasingly echogenic as a result of tubular and interstitial deposition of calcium, uric acid, and glycogen. Increased medullary echogenicity can be punctate or diffuse and is typically progressive and unaffected by therapy. Both nephrocalcinosis and renal calculi can develop.[171,175]

Tamm–Horsfall Proteinuria and Other Inspissation Syndromes

Transient medullary hyperechogenicity as a result of intratubular inspissation of the Tamm–Horsfall protein, also known as uromodulin, has been reported in 3%–5% of otherwise healthy term neonates during the first week of life.[176,177] At US, the pyramids can appear diffusely speckled or the abnormality can appear as a splotchy hyperechoic focus involving the inner third of the pyramid, extending outward from the papillary tip. Discretion is needed, as the Tamm–Horsfall protein deposit within the renal calyces may look similar to nephrocalcinosis in some cases on renal US of neonates, and especially preterm infants.[171] The abnormality can be unilateral or bilateral and is visible shortly after birth. Despite the fact that the deposits can be quite conspicuous on US, they are not visible on nonenhanced CT. Physiologically, decreased tubular flow during the first days of postnatal life is thought to be important. The Tamm–Horsfall protein is known to precipitate and form intratubular aggregates when present in a larger than normal quantity. Urinary excretion of the Tamm–Horsfall protein is normally higher at

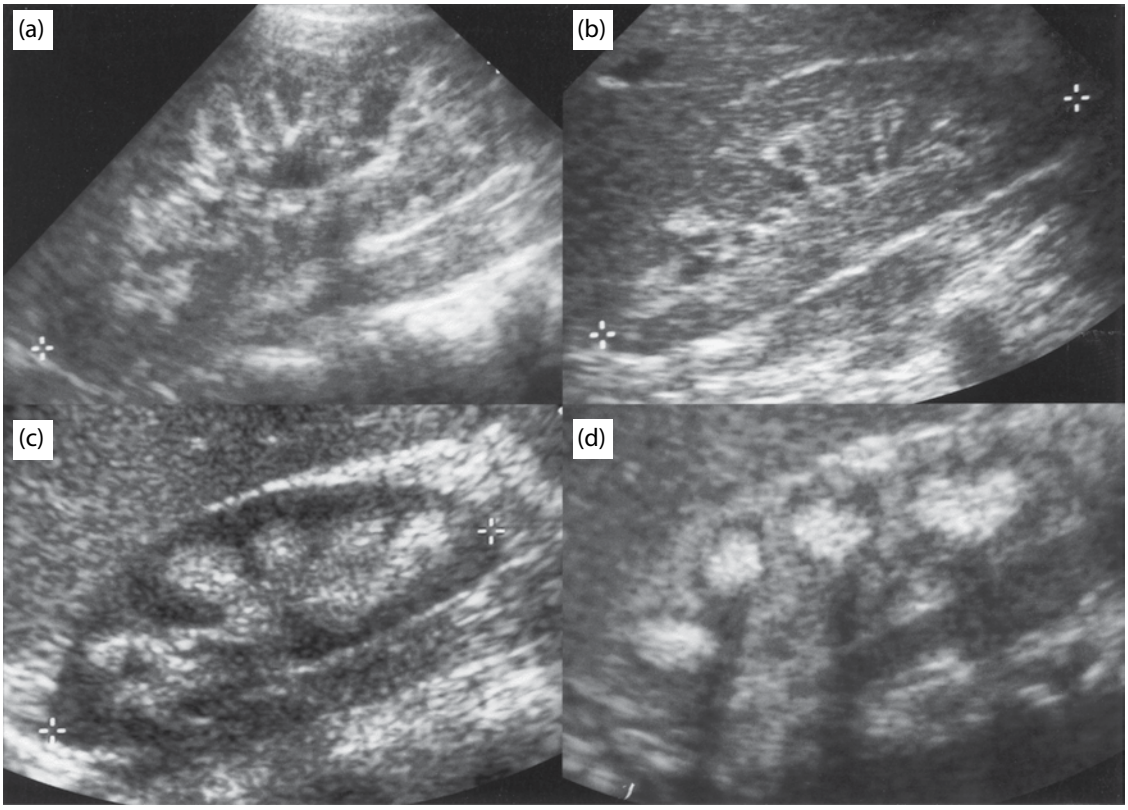

FIGURE 28.18 Sonographic patterns of medullary hyperechogenicity in nephrocalcinosis. (a) Longitudinal view of the left kidney in a 3-year-old girl with Williams syndrome shows thin, peripheral hyperechoic linear bands outlining the pyramids with the centers remaining hypoechoic. The cortex appears normal. (b) Longitudinal view of the right kidney in a 14-year-old boy with familial hypophosphatemic rickets shows thicker peripheral echogenic margins of the pyramids. Some pyramids appear almost uniformly hyperechoic. The cortex appears normal. (c) Longitudinal view of the right kidney in a 7-year-old boy with distal renal tubular acidosis shows diffusely and nearly homogeneously hyperechoic medullary pyramids. There is no posterior acoustic shadowing and the cortex appears normal. (d) Longitudinal view of the right kidney in a 7-week-old girl with severe idiopathic hypercalcemia shows very intense, diffuse medullary hyperechogenicity with posterior acoustic shadowing. The cortex is also thin and echogenic, consistent with cortical nephrocalcinosis.

birth and declines during the first week. Some authors have reported a temporal relationship between the disappearance of hyperechogenicity and the establishment of a consistent pattern of micturition toward the end of the first week of life. Similar sonographic appearances have been reported in children and adults with oliguric renal failure and persistently increased urinary Tamm–Horsfall excretion.[27] Medullary hyperechogenicity is also observed in patients with intratubular deposition of other large macromolecules, such as in rhabdomyolysis, myoglobinuria, and toxic shock syndrome, and in children with leukemia and tumor lysis syndrome. The resistive index is usually increased on Doppler US, and renal dysfunction is common. The reversibility of US findings depends on reestablishment of a normal urine flow rate.

Renal Cystic Diseases

US is the primary imaging modality that is used in renal cystic diseases.[21,22,27,178] CT and MRI are generally reserved for those cases in which either the sonographic appearance is uncertain or complications, such as cystic rupture, hemorrhage, or neoplasm, are suspected. Because isolated, simple renal cysts occur only very rarely in children,[21,22,179,180] the presence of renal cysts in a child should at least lead to consideration that these might be an underlying renal disorder, such as renal dysplasia. On the other hand, many renal lesions that appear cystic on US in children are often not cysts. For example, caliceal diverticula, dilated calices, and even very prominent and hypoechoic medullary pyramids should not be mistaken for cysts. On US, renal cysts appear as round or ovoid, thin-walled, fluid-filled structures.[27,67,178–180] The fluid within uncomplicated cysts is anechoic, and the wall is thin and slightly hyperechoic. Cellular, purulent, or proteinaceous debris or blood clot in complicated cysts causes the fluid to appear more echogenic. Particular debris within the cyst fluid is best visualized with US. The fluid in uncomplicated cysts appears homogenous with low attenuation on CT, and has a low signal intensity on spin-echo and inversion recovery T1-weighted magnetic resonance images.[58,181,182] On spin-echo T2-weighted images, the signal intensity of the fluid increases and the wall of the cyst and the fluid may not be distinguishable. Although larger clots within cysts can often be identified with CT, differences in fluid composition and small debris within cyst fluids are more readily identified with MRI. The signal intensity in hemorrhagic cysts is generally brighter and more heterogeneous on both T1- and T2-weighted

images, but can vary considerably depending on the age of the hemorrhage and the relative proportions of hemoglobin, deoxyhemoglobin, and hemosiderin. On children, mural calcification is rare in renal cysts, although it is well described in adults. Mural calcifications are best evaluated with CT or US, although larger calcifications are sometimes identifiable with MRI as a signal void within the cyst wall.

Caliceal Diverticulum

Caliceal diverticula are a urothelium-lined, saccular, outpouching of the collecting system that typically arises from one of the caliceal fornices.[58,176,183,184] Caliceal diverticula are believed to be congenital lesions. Rarely, a cyst hematoma, or abscess that ruptures into a calyx, will form a permanent communication with the collecting system and can be indistinguishable from a congenital diverticulum. On US, a caliceal diverticulum appears as a cystic lesion and is characteristically located centrally in the kidney, adjacent to the pyramids and collecting system.[58,176,183,184] Caliceal diverticula range in size from several millimeters to many centimeters. Individual diverticula can also vary considerably in size, depending on the degree of distention. Most diverticula communicate freely with the collecting system and will be opacified during either anterograde or retrograde urography, as well as during contrast-enhanced CT and MRI.[185] However, when the neck of the diverticulum is stenotic, the fluid within the diverticulum will opacify only faintly or not at all. Comparing the attenuation within the diverticulum on nonenhanced images with similar measurements on delayed contrast-enhanced images may increase the chance of detecting faint opacification in a stenotic diverticulum. For this reason, use of sonography may be insufficient for accurately diagnosing this condition, requiring retrograde or anterograde contrast urography or contrast-enhanced CT, or both.[198] On nonenhanced CT and MRI, caliceal diverticula will similarly be difficult to differentiate from other centrally located cystic lesions.

Autosomal Recessive Polycystic Kidney Disease

Autosomal recessive polycystic disease is caused by mutations in a single gene, PKHD1[186] (polycystic kidney and hepatic disease). This disease is manifested by bilateral severe dilation and ectasia of the interstitial portion of the collecting tubes.[162,187] On US, the kidneys are usually dramatically enlarged, heterogeneous, and echogenic.[27,67,179,188,189] The echogenic appearance of the parenchyma relates to the abnormally enhanced reflection of sound waves of the walls of the distended and ectatic tubules. The compressed renal cortex is studded with innumerable tiny cysts and appears as a relatively hypoechoic marginal halo around the kidney and occasionally around the individual renal lobes (Figure 28.19).[188–190] The same architectural changes are visible on CT, with relatively poorly enhancing ectatic tubules producing a peripherally radiating striated appearance to the enlarged central portions of the individual renal lobes surrounded by brightly enhancing compressed cortex studded with countless tiny cysts.[58]

Autosomal Dominant Polycystic Kidney Disease

Autosomal dominant polycystic kidney disease is recognized as a monogenic disorder caused by mutations in two genes: PKD1, which accounts for 85% of cases, and PKD2, which accounts for 10% of cases.[185] When autosomal dominant polycystic kidney disease presents in childhood, the cysts are usually small, bilateral, and few in number.[21,27,58,179] In neonates, the kidneys appear large and contain multiple small cysts, mimicking the appearance of the recessive form of the disease.[191–195] As the child becomes older, the cysts increase in size and number. Mural calcification is rarely seen in children. Complications such

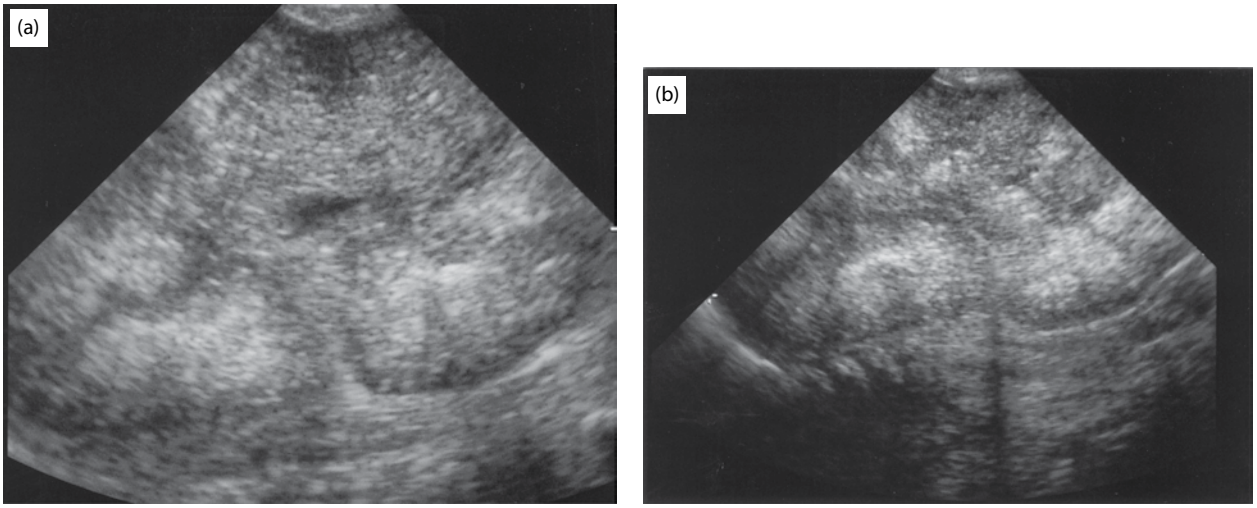

FIGURE 28.19 A newborn boy with autosomal recessive polycystic kidney disease. Ultrasound shows markedly enlarged kidneys, with accentuation of the renal lobar anatomy. The medullary portions of the renal lobes appear enlarged and very echogenic and are surrounded by a thin peripheral cortical halo. No larger macrocysts are visible. (a) Ultrasound: longitudinal view of the right kidney (length 12.7 cm). (b) Ultrasound: longitudinal view of the left kidney (length 13.2 cm).

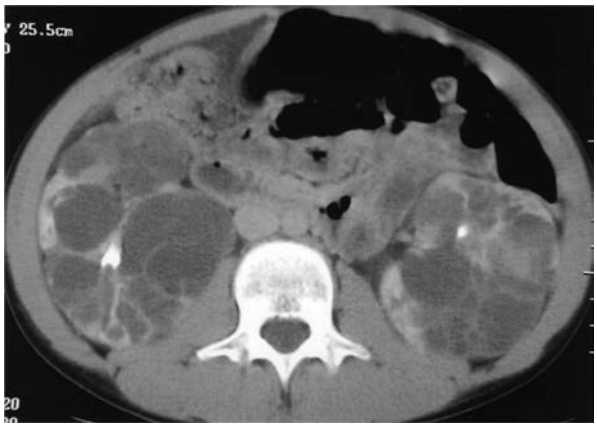

FIGURE 28.20 A 12-year-old girl with autosomal dominant polycystic kidney disease, presenting with abdominal pain and hematuria after a minor motor vehicle accident. Contrast-enhanced CT shows the kidneys to be almost entirely replaced by numerous large cysts, with strands of residual enhancing parenchyma visible between the cysts.

as a hemorrhage within a cyst can be visualized on either CT or MRI (Figure 28.20). MRI often shows striking differences in the signal intensity of the fluid in the cysts, reflecting differences in protein of the fluid.[196]

Glomerulocystic Disease of the Kidney

Glomerulocystic kidney disease presents as a cystic dilation of the space within Bowman's capsule surrounding the glomeruli on histology.[197] Glomerulocystic kidney disease is a rare disorder that is frequently indistinguishable, based on its imaging and clinical features, from classic recessive polycystic disease in the neonate and from other cases of dominant polycystic kidney disease. Autosomal dominant transmission has been suggested in some lineages, with the parents of the affected infants presenting with the classic dominant polycystic disease imaging. Liver disease similar to that in recessive polycystic disease can also occur. Glomerulocystic disease can also occur in trisomy 13, oro-facial-digital syndrome, Zellweger syndrome, tuberous sclerosis, and Meckel–Gruber syndrome, and similar histologic changes are seen in some patients with renal dysplasia. Such widespread clinicopathologic overlap has led some clinicians to suggest that glomerulocystic disease might in reality represent a nonspecific histologic appearance rather than a specific disease.[198] Countless small cysts, with a predominantly cortical and subcapsular distribution, are found in glomerulocystic diseases on US.[27,189,199–203] Bilateral renal enlargement in neonates is common, although not as dramatic as in classic recessive polycystic disease.[203] The kidneys can decrease in size over time without apparent deterioration in renal function. In other cases, the appearance progresses over time to that of dominant polycystic disease. Furthermore, glomerular cysts are often small; thus, high-resolution US or very thin-sliced CT may be needed, along with MRI, to confirm the diagnosis.[203] Because of the considerable overlap in the imaging appearance between this disorder and other more common forms of polycystic kidney disease, definitive diagnosis may ultimately require biopsy or a genetic testing.

Medullary Cystic Disease

Juvenile nephronophthisis and adult-onset medullary cystic disease of the kidney are both familiar forms of chronic tubulointerstitial nephritis that are associated with a urinary concentrating defect and progressive azotemia.[27,144,202,204–206] Medullary cysts are present in both diseases. However, the clinical manifestations and patterns of transmission are different. Juvenile nephronophthisis is an autosomal recessive disorder that primarily affects children and is characterized clinically by polyuria, growth failure, and progressive renal insufficiency, usually leading to death in later childhood. Juvenile nephronophthisis is frequently associated with a variety of extrarenal manifestations, including retinitis pigmentosa, cone-shaped epiphyses, hepatic fibrosis, and cerebella aplasia. Adult medullar cystic disease is an autosomal dominant disorder with no extrarenal involvements that typically presents in the third decade of life or later and is rarely diagnosed in children. In juvenile nephronophthisis, the kidneys are small or normal in size on US, with diffusely increased parenchymal echogenicity and medullary cysts.[27,177,178,197] Although medullary cysts are regarded as a characteristic sonographic feature of juvenile nephronophthisis, increased parenchyma echogenicity with loss of corticomedullary differentiation can precede development of visible macrocysts, resulting in a nonspecific appearance in some patients. Very thin-section (1.5 mm) CT or MRI can confirm the presence of medullary cysts in children with atypical sonographic appearances.[144,202,205,207]

Medullary sponge kidney is a rare, nonhereditary disorder of unknown causes that is characterized by nonprogressive medullary ductal ectasia, renal tubular acidosis, hypercalciuria, and nephrocalcinosis.[27,208,209] On excretory urography, the appearance reflects the severity of the ductal ectasia.[210] In very mild cases, the medulla has a thin, striated appearance. With more severe involvement, the linear medullary striation first becomes thicker and then cystic in appearance. Small calculi from within the tubules and the papillae enlarge as the calices become progressively more distorted. In most advanced cases, abdominal radiographic studies reveal nephrocalcinosis or nephrolithiasis, or both. The appearance of multiple clusters of tiny calculi overlying the medullary pyramids is diagnostic of medullary sponge kidney. Calculi that have eroded into the collecting system are visible in the renal pelves, ureters, or bladder. On US, renal size is normal and the medullary pyramids appear hyperechoic as a result of intraluminal calcium deposition.[27,163,210] Shadowing intratubular calculi appear later in the disease. CT is generally inferior to excretory urography in detecting tubular ectasis in medullary sponge kidney and is invariably normal early in the disease. However, nonenhanced CT may be better in identifying small intratubular calculi that would be obscured by contrast material on excretory urography.

Renal Dysplasia and Multicystic Dysplastic Kidney

Normal nephroureteral development entails a series of complex interactions between the ureteric bud and the developing metanephros, beginning in the seventh

gestational week. Failure of these interactions to proceed normally can result in renal dysplasia. Although renal dysplasia is frequently associated with congenital obstructive uropathy,[164,211,212] it can also occur in the absence of detectable obstruction in patients with severe VUR and as an isolated anomaly.[23,212–215] On US, dysplastic kidneys are usually small for age or body size and grow slowly.

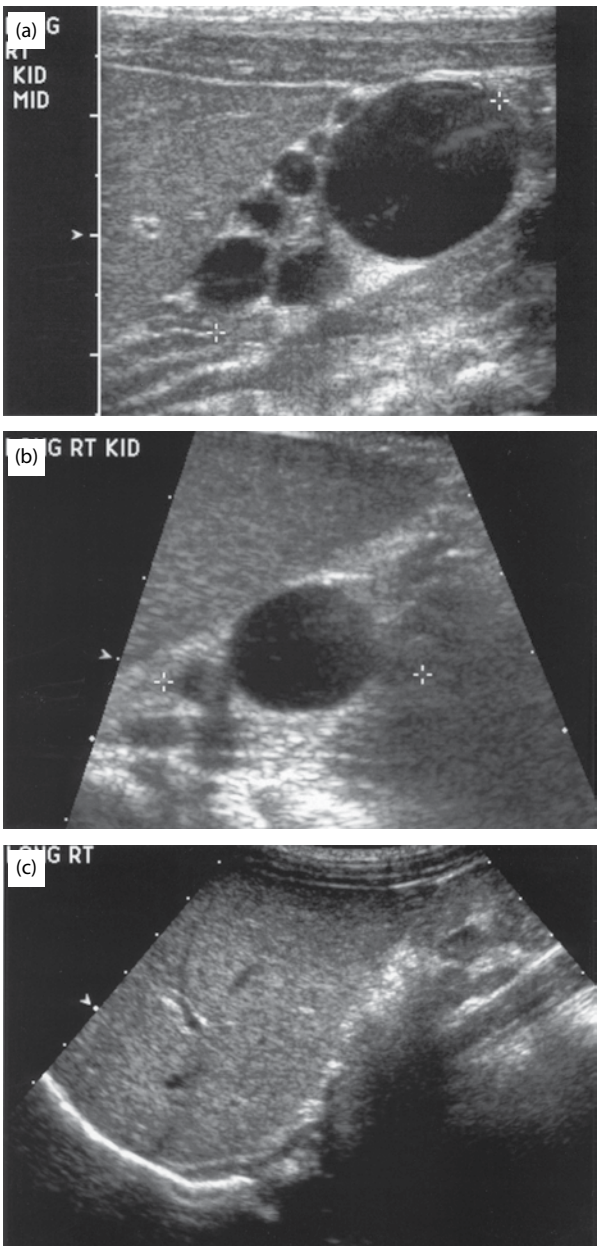

FIGURE 28.21 A newborn boy with right multicystic dysplastic kidney and subsequent involution. (a) Ultrasound: longitudinal view of the right kidney at 2 days old shows the right kidney (length 4.2 cm) is entirely replaced by multiple non-communicating cysts of different sizes separated by thin bands of echogenic, dysplastic parenchyma. (b) Ultrasound: longitudinal view of the right kidney at 8 months old shows all of the cysts have decreased in size and the kidney now measures 3.1 cm in length. (c) Ultrasound: longitudinal view of the right renal fossa at 18 months old shows no residual visible cysts or right kidney.

The renal parenchyma appears abnormally echogenic, with reduced or absent corticomedullary differentiation.[21,22,27,215–217] Cysts are present in 40%–50% of cases. In the cases of severe dyplasia associated with obstruction, the collecting system can be dysmorphic, with poor differentiation of calices, infundibula, and renal pelvis.[22] When cysts or hydronephrosis are present, the renal measurement may underestimate the reduction in total renal parenchymal volume.[213] On scintigraphy, the dysplastic kidneys typically have reduced function, although complete absence of function is uncommon, a feature that is important in distinguishing typical renal dysplasia from multicystic dysplastic kidney (MCDK). Although the US findings of small, echogenic kidney that functions poorly on scintigraphy is usually diagnostic of dysplasia in the neonate, this sonographic appearance is not specific. In an infant or child, a variety of chronic and atrophic renal parenchymal disorders, including interstitial nephritis and chronic glomerulonephritis, are indistinguishable from renal dysplasia in the absence of suggestive or historical or biochemical information or previous imaging studies.[22,216,217]

In MCDK, atresia of the ureteral bud at or just below the ureteropelvic junction early in nephrogenesis results in a severely dysplastic, nonfunctioning, cystic kidney.[22,218–220] The diagnosis of MCDK is usually easily established based on characteristic imaging findings on US and renal diuretic or cortical scintigraphy of a nonfunctioning kidney that is replaced by multiple noncommunicating cysts with no residual normal-appearing parenchyma.[22,220] On CT and MRI, the kidney is replaced by multiple cysts of different sizes that are separated by a small amount of nonfunctioning dysplastic parenchyma (Figure 28.21). In the hydronephrotic variant of multicystic dysplasia, the kidney is nonfunctioning and contains one or more small peripheral cysts, with a large central cyst representing a rudimentary, dilated collecting system.[213,214,219] In segmental MCDK, the anomaly affects only one moiety of a partially or completely duplicated collecting system. When bilateral, MCDK is incompatible with extrauterine life and is usually accompanied by severe oligohydramnios, pulmonary hypoplasia, and other features of Potter's syndrome.

In most patients with MCDK, the fluid within the cysts is gradually absorbed and the kidney progressively decreases in size until it is no longer identifiable on US (Figure 28.21).[207,221–223] Because the dysplastic renal remnant has no function, it will not be identifiable on renal scintigraphy. This process of "involution" ultimately results in an appearance that is indistinguishable from unilateral renal agenesis.[224]

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CHAPTER 29

Assessment of Renal Obstructive Disorders: Ultrasound, Nuclear Medicine, and Magnetic Resonance Imaging

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INTRODUCTION

The widespread use of maternal sonography and the routine radiographic evaluation of children with febrile urinary tract infections have resulted in the increased diagnosis of both antenatal and postnatal hydronephrosis. Hydronephrosis is the most common abnormality detected by prenatal ultrasound (US) and is seen in an estimated 1 in 100 to 1 in 500 pregnancies.[1] One of the most important distinctions in the assessment of these children is determining which patients would benefit from surgery and which can be safely observed. This distinction is important since unnecessary intervention exposes patients needlessly to the morbidity of surgery, whereas inappropriate observation places patients at risk for infection and renal parenchymal loss.

The common pediatric renal obstructive disorders are listed in Table 29.1. Of these, ureteropelvic junction obstruction (UPJO) is the most common and accounts for nearly half of all prenatally detected uropathies.[1] Ureterovesical junction obstruction (UVJO), ureteroceles, and ectopic ureters are responsible for the majority of the remaining cases. The natural history of renal pelvic dilatation is largely related to the underlying diagnosis. For example, hydronephrosis secondary to an ectopic ureter is unlikely to resolve spontaneously, whereas patients with megaureter can often be followed for years without renal functional loss.[2] The outcome of patients with UPJO is more variable, and as a result, management is more controversial. Some clinicians recommend early surgery, whereas others advocate simple observation.[3–5] Regardless, most urologists will initially follow hydronephrotic kidneys conservatively and use decreasing differential renal function (DRF) or worsening hydronephrosis as an indicator that surgery may be required. Radiographic approaches to the diagnosis and assessment of renal obstructive disorders have evolved significantly over the past several decades. Intravenous urography (IVU) and the antegrade pressure–flow test, referred to as the Whitaker test, were once mainstays in the evaluation of these patients and are now only rarely used. Technologic advances have given way to US, diuretic renal scintigraphy (DRS), and more recently, magnetic resonance imaging (MRI) for the evaluation of hydronephrosis. Voiding cystourethrography (VCUG) is frequently performed in conjunction with these studies to rule out vesicoureteral reflux (VUR) as the cause of hydronephrosis. Each of these diagnostic modalities has relative advantages and disadvantages (Table 29.2). In general, these studies provide either good anatomic or good functional information, whereas none of these studies, save MRI, provide both. Some tests are more invasive than others, which also influences test selection. Currently, no study is considered a gold standard for the evaluation of renal obstructive disorders, and complete assessment typically involves a series of studies, including US, VCUG, and DRS. Consequently, a thoughtful diagnostic strategy is necessary to proceed with appropriate management at minimal cost and morbidity to the patient.

TABLE 29.1 Causes of pediatric hydronephrosis

Obstructive causes
• Ureteropelvic junction obstruction
• Ureterovesical junction obstruction
• Ectopic ureters
• Ureteroceles
• Posterior urethral valves
• Urethral atresia
• Anterior urethral valves
• Congenital urethral stricture
Nonobstructive causes
• Vesicoureteral reflux
• Primary nonobstructive megaureter
• Megacalicosis
• Fetal folds
• Neurogenic bladder
Conditions mimicking hydronephrosis
• Extrarenal pelves
• Multicystic dysplastic kidney
• Peripelvic cysts
• Neonatal kidneys (hypoechoic renal pyramids)

TABLE 29.2 Advantages and disadvantages of various diagnostic modalities for the assessment of renal obstructive disorders

Imaging study	Advantages	Disadvantages
Intravenous pyelography	Good anatomy if function is good	Inaccurate if poor function; nephrotoxic contrast; radiation exposure
Whitaker test	Only study that measures directly the pressure in the renal pelvis/bladder	Invasive; not reproducible; no functional information; radiation exposure
Ultrasound	Inexpensive; portable; no contrast or radiation exposure	No functional information; limited anatomy
Diuretic renal scintigraphy	Good functional and drainage information	Limited information in bilateral disease; no anatomic information; interpretative error; 15% false negatives/positives
Gd-MRU	Superior anatomic and functional information even if poor function or bilateral disease; no radiation; contrast nonnephrotoxic	Expensive; not yet widely available; requires sedation and monitoring

ULTRASONOGRAPHY

Ultrasonography (US) constitutes a cornerstone in the radiologic evaluation of renal obstructive disorders. It is noninvasive, inexpensive, and portable; does not require ionizing radiation or contrast media; and is not limited by renal failure. As a result, US is ideally suited as a screening study and for following patients with known abnormalities. A properly performed study provides information regarding renal size, cortical thickness and architecture, and the degree of dilatation of the collecting system. Nomographic charts are available that give "normal" renal lengths for children of varying ages and body weights (Figure 29.1). The sonographic examination, however, is operator dependent, and a skilled sonographer is essential for informative and reproducible studies. The US examination may be limited by body habitus, overlying bowel gas, and poor patient cooperation.

The hallmark finding of hydronephrosis on US is separation of the hyperechoic central renal sinus by anechoic branching structures that represent the dilated calices. With more chronic and severe forms of hydronephrosis, cortical thinning may be seen. Often, if the process is unilateral and leads to renal parenchymal loss, the contralateral kidney may undergo compensatory hypertrophy in young children. In moderate and severe UPJO, pronounced caliceal and renal pelvic dilatation may occur, giving the kidney a classic "bear paw" appearance on US (Figure 29.2). The ureters can usually only be seen on US if they are dilated, and the presence of a dilated ureter lying posterior to the bladder helps distinguish megaureter from UPJO. When either diagnosis is a consideration, a VCUG to rule out VUR as the cause of dilatation should be performed. It should be kept in mind that VUR may coexist with UPJO in as many as 10% of children.[7]

The Society for Fetal Urology (SFU) has proposed a grading system for reporting hydronephrosis detected by US.[8] This system takes into consideration the appearance of the calices, renal pelvis, and parenchyma to grade the degree of hydronephrosis from 0 to 4 (none to severe). SFU grades 1 and 2 represent mild to moderate degrees of pelviectasis and should not be considered hydronephrosis. Grades 3 and 4 represent true hydronephrosis, with grade 4 being the most severe, with cortical atrophy (Table 29.3). The degree of hydronephrosis is used to assist in decision making with regard to treatment and, additionally, provides some prognostic information. For example, SFU grades 1 and 2 hydronephrosis secondary to UPJO have a tendency to resolve with time and usually only require a VCUG to rule out VUR and sonographic reevaluation. For SFU grades 3 and 4, some type of functional evaluation, in addition to a VCUG, is usually recommended since these patients are more likely to have significant urologic pathology and to require surgical intervention.

There is a well-documented correlation between the anteroposterior diameter (APD) of the renal pelvis on prenatal US and the probability that a significant postnatal pathology will be present. Although controversy exists over cutoffs for abnormal and normal APDs, most authors agree that an APD of <4 mm is considered normal and that an APD of >15 mm represents severe hydronephrosis. The SFU published a consensus statement that is based on a meta-analysis and suggests how to evaluate and manage antenatal hydronephrosis.[9] Antenatal hydronephrosis grading by APD and gestational age is summarized in Table 29.4. Mild, moderate, and severe hydronephrosis carry a risk for postnatal pathologies in 12%, 45%, and 88%, and consequently, postnatal evaluation varies according to the degree of antenatal hydronephrosis.[10] UPJO is found in 5%, 17%, and 54% in mild, moderate, and severe antenatal hydronephrosis, while VUR occurs in 5%, 14%, and 9%.[10]

The term *hydronephrosis* implies obstruction, and exposes an important limitation of US. No functional information is obtained from conventional US, and obstruction cannot be diagnosed based solely on anatomic information. Therefore, although US is highly accurate in the diagnosis of renal dilatation, it is not reliable in predicting obstruction or providing information regarding renal function. Even in the presence of renal pelvic dilatation secondary to an obstructive process, the degree of dilatation does not necessarily reflect the degree of, or functional significance of, the obstruction. Indeed, numerous cases have been reported of mild dilatation with complete obstruction and marked dilatation when no obstruction is present. False-positive studies may result

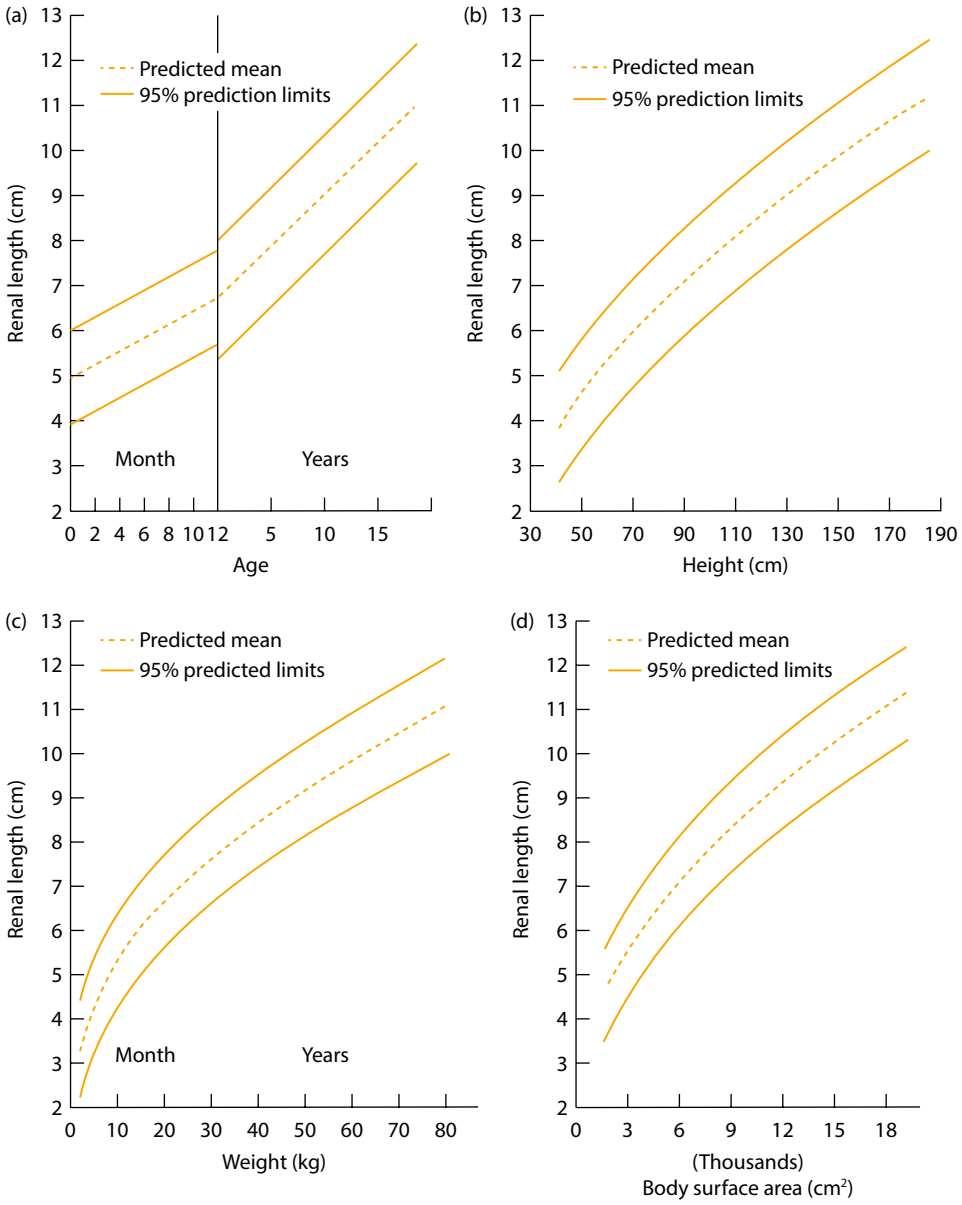


FIGURE 29.1 Renal nomographic chart. (Adapted from Han BK, Babcock DS. *AJR Am J Roentgenol* 1985;145:611–6.)

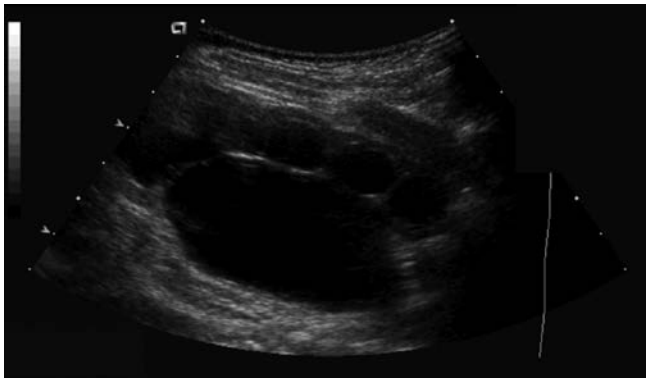


FIGURE 29.2 A 2-week-old boy with left UPJO. Note the massive renal pelvic and caliceal hydronephrosis, giving the kidney the appearance of a bear paw on US.

TABLE 29.3 SFU grading scale for hydronephrosis detected by US

Grade	Central renal echo complex (Pelvis and calices)	Renal parenchyma
0	No splitting	Normal
1	Slight splitting	Normal
2	Further dilatation of pelvis and single or few dilated calices	Normal
3	Dilated pelvis and all calices dilated	Normal
4	Dilated pelvis and all calices dilated	Thinned

Source: Fernbach SK et al. *Pediatr Radiol* 1993;23(6):478–80.

TABLE 29.4 Definition of antenatal hydronephrosis by gestational age and APD

Degree of antenatal hydronephrosis	Second trimester	Third trimester
Mild	4 to <7 mm	7 to <9 mm
Moderate	7 to ≤0 mm	9 to ≤15 mm
Severe	>10 mm	>15 mm

Source: Nguyen HT et al. *J Pediatr Urol* 2010;6(3):212–31.

from an extrarenal pelvis, a peripelvic cyst, residual dilatation from previous obstruction, dilatation resulting from VUR, and pyelonephritis. The fetal and neonatal kidney may also appear hydronephrotic on US secondary to the hypoechoic appearance of the medulla and pyramids (Figure 29.3). False-negative studies are less frequent, but obstruction may be present in the absence of dilatation in acute obstruction and in certain extrinsic processes, such as metastases and retroperitoneal fibrosis. Oliguric states may also lead to false-negative studies. This is particularly true in the newborn, in whom renal sonography may underestimate or completely overlook renal dilatation because of the oliguric state of the healthy newborn. It is rare that this results in missing significant renal obstruction, however.

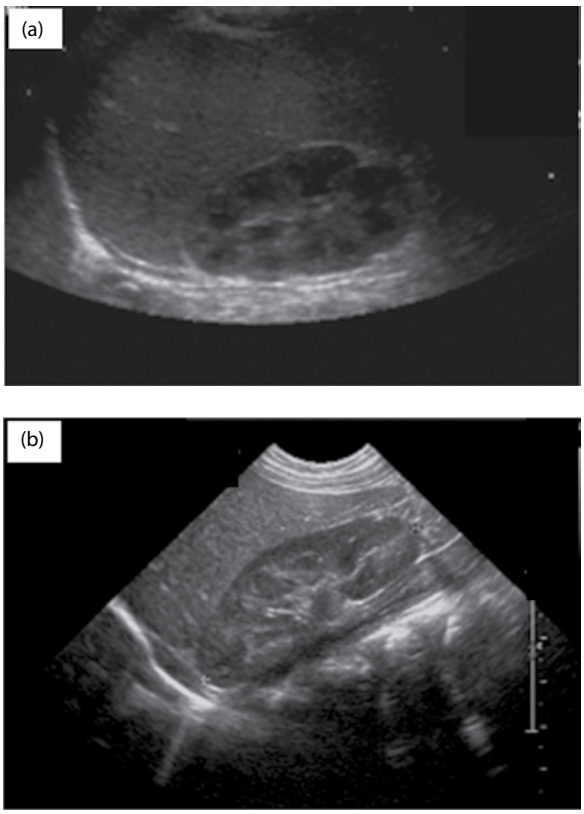


FIGURE 29.3 Right kidney of a 3-week-old by US. (a) Note the relatively hypoechoic renal pyramids, which may be mistaken for hydronephrosis. (b) Follow-up US 15 months later demonstrates resolving hypoechogenicity.

REFINEMENTS OF ULTRASONOGRAPHY

Given the limitations of conventional US in distinguishing obstructive from nonobstructive causes of hydronephrosis, several sonographic techniques have been developed in an effort to improve the diagnostic accuracy of US. Due to their high operator dependence, poor predictive value, and inconsistent study results, these techniques are rarely applied today. Among these methods, Doppler US with calculation of the resistive index (RI) has been shown to have some value in the diagnosis of renal obstructive disorders. This adjunct to US is based on the fact that obstruction causes an increase in intrarenal arterial resistance, resulting in a relative reduction in diastolic flow compared with systolic flow. Renal arterial resistance is quantified using the formula

$$\frac{\text{Peak systolic velocity} - \text{Minimum diastolic velocity}}{\text{Peak systolic velocity}}$$

The result of this formula is referred to as the RI (Figure 29.4). Different criteria have been proposed to suggest obstruction, including an RI of >0.70, an interrenal RI difference of >0.06–0.10 with unilateral dilatation, and an abnormal RI response to a diuretic challenge.[11] For children, and especially the neonate and infant, the RI tends to be elevated compared with adult standards. RIs of 0.7–1.0 can be normal in these populations and usually decrease to adult ranges by about 2–4 years of age.[12] Therefore, the latter two criteria appear most helpful in the pediatric age group.

Another sonographic modality is based on the determination of renal longitudinal parenchymal area and renal longitudinal pelvicaliceal area by computer planimetry. The ratio of parenchymal-to-pelvicaliceal area less than 1.6 was found to be predictive of renal obstruction and the need for subsequent pyeloplasty.[13] Diuretic Doppler US seeks to assess the significance of UPJO with a fluid challenge by evaluating the RI of the intrarenal vasculature

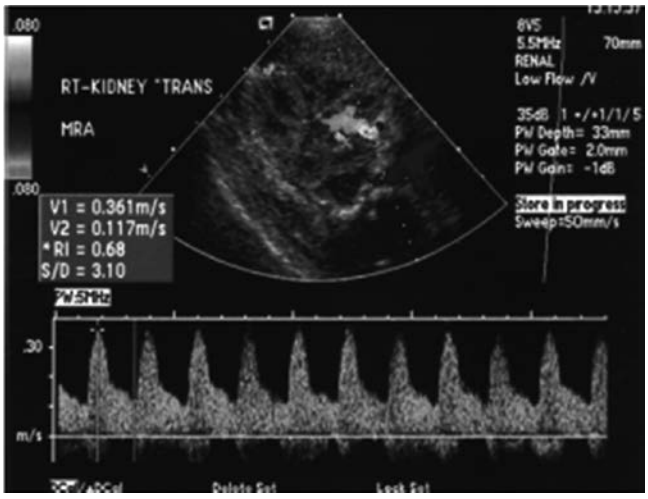


FIGURE 29.4 Duplex Doppler image taken from a 4-year-old boy. Note the arterial waveform and the normal RI of 0.68 (asterisk).

before and 10 minutes after administration of furosemide. A small study of 10 patients demonstrated that the preoperatively measured abnormal RIs were reversed after pyeloplasty.[14] Determination of APD or pelvicaliceal area yields one- or two-dimensional values and consequently does not account for the often disproportionately dilated three-dimensional (3D) collecting system. In order to determine the degree of dilatation of the entire pelvicaliceal space 3D US has been recently applied in prenatal and postnatal studies.[15] In a postnatal study, the renal parenchymal volume obtained by 3D US compared well with measurements obtained by magnetic resonance urography (MRU) and with DRF determined by renal scintigraphy.[16]

In summary, US is most commonly utilized as a screening method for the diagnosis of renal obstructive disorders. Although in theory duplex Doppler US can provide useful functional information, in practice other studies are used to better delineate the cause and functional significance of hydronephrosis once it is detected. Most commonly, after VUR has been ruled out by VCUG, the next study of choice is DRS.

DIURETIC RENAL SCINTIGRAPHY

DRS was developed in the late 1970s as a noninvasive method for evaluating patients with renal obstructive disorders. The introduction of better radiopharmaceuticals and gamma cameras has led to an increased use of nuclear imaging in pediatric urology. Once hydronephrosis is detected by other imaging methods, usually US, DRS is considered by many to be the preeminent method for estimating DRF and characterizing the severity of obstruction. Worsening renal function by DRS is often the impetus for pyeloplasty in patients being observed with UPJO. DRS also remains the most commonly used method for serial follow-up and postoperative assessment of patients with UPJO and megaureter.

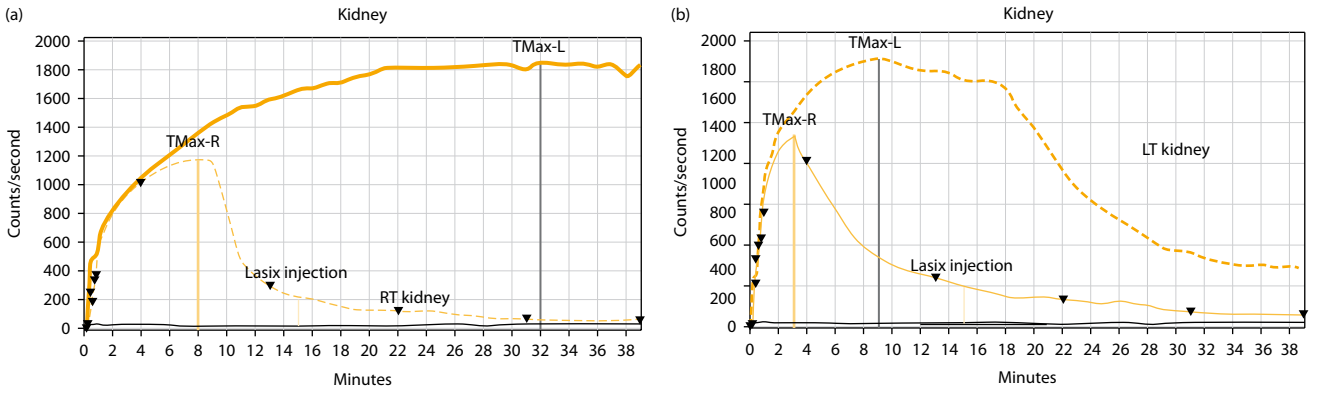
The radiopharmaceuticals used for DRS comprise a radionuclide, most commonly technetium 99m (^{99m}Tc), bound to a carrier macromolecule. Renal handling of the various radiopharmaceuticals, and therefore the information gained from DRS, is dictated solely by the biochemical properties of the carrier macromolecule. The ability to label these macromolecules, which have known physiologic destinations within the body, forms the basis of renal scintigraphy. The principal radiopharmaceuticals used for DRS are ^{99m}Tc mercaptoacetyltriglycine (MAG3) and ^{99m}Tc diethylenetriamine pentaacetic acid (DTPA) (Table 29.5). ^{99m}Tc MAG3, one of the newest radiopharmaceuticals, is 90% bound to plasma proteins and is principally cleared by tubular secretion. It shows both the parenchyma and collecting system well and provides excellent functional quantification. These qualities and the fact that it requires lower radiation doses than other radiopharmaceuticals make it the current agent of choice for evaluating renal function and drainage. In contrast, ^{99m}Tc DTPA has little plasma protein binding and is cleared almost exclusively by glomerular filtration. It is rapidly filtered into the urine and therefore provides excellent visualization of the pelvicaliceal system, ureter, and bladder, but may not be retained in the renal parenchyma long enough for good visualization of parenchymal abnormalities. Also, since ^{99m}Tc DTPA relies principally on glomerular filtration, results are often suboptimal in infants with immature kidneys and a low glomerular filtration rate (GFR) or in patients with compromised renal function. In these scenarios, ^{99m}Tc MAG3 is the preferred agent. ^{99m}Tc dimercaptosuccinic acid (DMSA) is unique among the other commonly used radiopharmaceuticals in that it tightly binds to the renal tubular cells and only a small amount is excreted into the urine. Therefore, it allows excellent visualization of the renal parenchyma and is primarily used for evaluating cortical lesions, such as scars that occur as a result of pyelonephritis.

TABLE 29.5 Common radiopharmaceuticals used in renal scintigraphy

Radiopharmaceutical	Renal handling	Application
^{99m}Tc MAG3	Principally cleared by tubular secretion	Renography
^{99m}Tc DMSA	Localizes and binds to the proximal convoluted tubules	Renal parenchymal imaging
^{99m}Tc DTPA	GFR dependent for clearance	Renography

The basic principles of DRS are as follows. The radiopharmaceutical of choice is injected intravenously. Normally, during the first 2–3 minutes, renal parenchymal uptake occurs. The radionuclide emits gamma radiation that is detected by a gamma counter. This emitted radiation is temporally and spatially quantified with computer-assisted digital processing and represented morphologically and graphically as a scan (Figure 29.5). This information is analyzed and compared, allowing for the computation of DRF. It is generally accepted that the error in determining the DFR is ±5%. After about 20 minutes, furosemide is injected intravenously to promote diuresis and the velocity and pattern of drainage from the kidneys to the bladder are analyzed. In the absence of obstruction, half of the radionuclide is cleared from the renal pelvis within 10–15 minutes, termed the $T_{1/2}$. A $T_{1/2}$ of >20 minutes indicates obstruction, whereas a $T_{1/2}$ of <15 minutes is generally considered normal. Times between 15 and 20 minutes are indeterminate. Indications for surgical intervention based on DRS generally include a DRF of <35–40% and a $T_{1/2}$ of >20 minutes, and US findings consistent with anatomic obstruction. Despite these parameters, neither should be used as an independent variable to determine if obstruction is present or absent.

Over the years, a wide variety of protocols and techniques for diuretic renography have been used. Unfortunately, this has produced variability in interpretation among different institutions. In an attempt to promote standardization of the technique, the SFU and the Pediatric Nuclear Medicine Council of the Society for Nuclear Medicine published guidelines for the "well-tempered" diuresis renogram in 1992.[17] Its purpose was to allow easy comparison between studies and institutions. The guidelines standardize many of the facets of the study, including intravenous hydration, bladder catheter placement, patient



	Right	Left
DRF	50%	50%
Tpeak	8 min	38 min
$T_{1/2}$	11 min	>30 min
Wash-out	98%	0%
Curve	Downsloping	Plateauing

	Right	Left
DRF	48%	52%
Tpeak	8 min	9 min
$T_{1/2}$	4 min	9 min
Washout	95%	77%
Curve	Downsloping	Downsloping

FIGURE 29.5 Diuretic renal scan (^{99m}Tc MAG3) taken from a 9-year-old boy with severe left UPJO (a) before and (b) after dismembered pyeloplasty. Note that preoperatively the $T_{1/2}$ of the left kidney is never reached.

position, data acquisition and analysis, timing of diuretic administration, and regions of interest (ROIs) for which to monitor the diuretic effect. However, in practice, local protocols are still frequently used, which makes comparing results from different centers problematic.

Despite the widespread use of DRS, there are significant limitations with the technique. For example, DRS only provides DRF and, as a result, is less informative in patients with overall poor renal function or solitary kidneys. Caution must be taken when interpreting results in these scenarios. Very capacious collecting systems can also prove problematic, since radionuclide retained in the renal pelvis may be included in the ROI and falsely elevate differential function. Although debatable, this artifact may be responsible for the supranormal function (>55%) reported for some hydronephrotic kidneys.[18] When dilated collecting systems are included in the ROI, the resulting renogram may be false positive for renal obstruction. To eliminate the confounding effects of slow radiotracer passage through a dilated pelvicaliceal system, careful ROI placement solely around the renal parenchyma was proposed. A review of a large number of ^{99m}Tc MAG3 renal scintigraphies revealed that if the renal parenchyma drained (i.e., downsloping curve), the kidney was not obstructed.[19] Another review from the same group suggested that ^{99m}Tc MAG3 renal scintigraphies performed in neonates do yield meaningful results even when the entire kidney is included in the ROI. While a downsloping renogram correlated with future resolution, an upsloping renogram was predictive of subsequent pyeloplasty.[20] Interpretation is also somewhat subjective and may lead to reporting error (Figure 29.6). Other disadvantages of DRS are its poor anatomic resolution and long examination times. Not infrequently, patients will fall into the equivocal category. These patients may require a repeat DRS or, less commonly, a Whitaker test, to further assess renal obstruction. Overall, DRS may fail to determine the presence or absence of obstruction in at least 15% of cases.[21]

Clearly, there are strengths and weaknesses associated with US and renal scintigraphy. Specifically, whereas US provides useful anatomic information, it provides no functional information. Conversely, renal scintigraphy provides functional information, but little anatomic information. Therefore, although these studies are highly informative in tandem, neither study alone is typically sufficient for making clinical decisions. Recently, contrast-enhanced MRI of the urinary tract, as a single study, has been shown to have promise in the investigation of renal obstructive disorders.

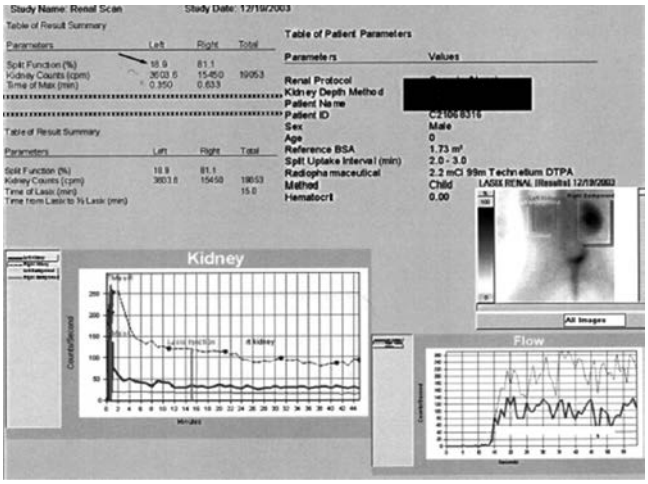


FIGURE 29.6 Diuretic renal scan from a 3-month-old boy. Note that the scan shows 18% differential left renal function. Further evaluation showed that the patient had a solitary right kidney, which highlights the interpretative error possible with scintigraphy.

MAGNETIC RESONANCE IMAGING

The use of MRU in the diagnosis of pediatric renal obstructive disorders has increased dramatically since it was introduced in the late 1980s. This has been the result of a series of recent technological advances that have enabled faster image acquisition, improved resolution, reduced motion artifact, and 3D reconstruction. Even today, newer imaging sequences and shorter acquisition times are improving image quality and expanding the diagnostic capabilities of MRU. The advantages of MRU for evaluating renal tract anomalies in children are that it has multiplanar capabilities, offers excellent anatomic resolution and soft tissue contrast, and does not use ionizing radiation. Possibly, one of the most important developments occurred in the late 1990s when gadolinium-DTPA (Gd-DTPA) was first used in conjunction with MRU. Gd-DTPA and ^{99m}Tc DTPA share the same carrier macromolecule and are handled by the kidneys in an identical fashion. As a result, Gd-DTPA-enhanced MRU (Gd-MRU) measurements of renal perfusion, uptake, and excretion correlate with those obtained by ^{99m}Tc DTPA renal scintigraphy. Gd-MRU is the only study to date that has the capability of providing excellent morphologic detail typical of MRI, as well as functional information that is equivalent or superior to DRS. Even at very low concentrations, Gd-DTPA has high signal intensity on MRI, giving Gd-MRU the ability to reliably detect hydronephrosis and transition in ureteral caliber even in nonfunctioning systems (Figure 29.7). The results of one study showed that Gd-MRU may be a useful tool for distinguishing an obstructed from a nonobstructed dilated system, even when ^{99m}Tc MAG3 renography results were compromised by reduced renal uptake in the affected kidney.[22] While gadolinium is not nephrotoxic per se, the use of gadolinium-based contrast agents in patients with renal failure has been linked to nephrogenic systemic fibrosis. This debilitating and, in 5% of cases, fatal disease can be avoided if safety guidelines are strictly followed.[23]

Although protocols for Gd-MRU differ slightly among institutions, the basic principles are preserved. The study involves initial T1- and T2-weighted images through the kidneys, ureters, and bladder. Gd-DTPA is then administered intravenously, and dynamic contrast-enhanced T1-weighted imaging using a volumetric gradient echo technique is performed over the entire urinary tract. In a fashion similar to IVU, the uptake, excretion, and drainage of Gd-DTPA can be visualized sequentially. The advantage of Gd-MRU is that, in addition to providing anatomic information that exceeds that of US, computer-assisted postprocessing techniques can be employed to objectively quantify function and the degree of obstruction, similar to DRS.

During postprocessing, image sequences are viewed as cinematic loops. This permits the assessment of renal perfusion and excretion and the generation of signal intensity versus time curves. Following contrast administration, three distinct phases of enhancement are recognized (Figure 29.8). In the first phase, the renal cortex enhances vividly, differentiating renal cortex from medulla. This is followed by a medullary phase, where the medulla enhances greater than the cortex. The third phase consists of excretion of contrast medium into the collecting system and ureters. Gadolinium transit through these anatomic areas causes a variation in the magnetic resonance signal intensity over time, which can be represented graphically by signal intensity versus time curves (Figure 29.9). When function is reduced in one kidney, signal intensity is reduced compared with the normal side. The 3D maximum intensity projection (MIP) images from delayed images of the renal pelvis and ureters that exhibit good contrast enhancement provide excellent anatomic resolution of the collecting system and ureters.

The diagnosis of obstruction on MRU is based morphologically on the findings of renal pelvic dilatation and ureteral narrowing. Functionally, obstruction is suggested by reduced enhancement, delayed excretion of contrast into the collecting system and ureter, swirling

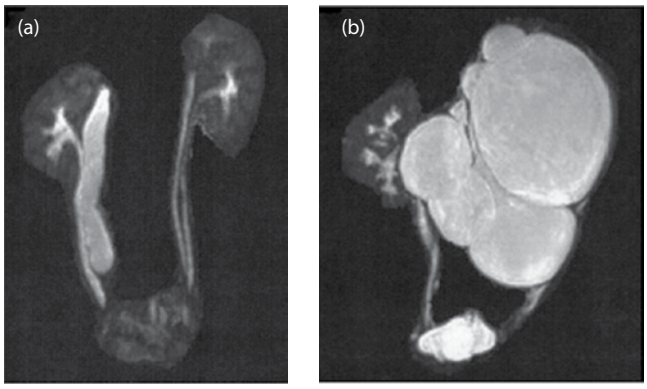


FIGURE 29.7 Gadolinium-enhanced MRU permits hydronephrosis and transition in ureteral caliber to be reliably detected even in nonfunctioning systems. (a) An 8-year-old patient with a dysmorphic right upper pole, with a dilated ureter down to the pelvis consistent with ureteral atresia. These findings could not be appreciated on either US or DRS. (b) Left multicystic dysplastic kidney that had no function on DRS.

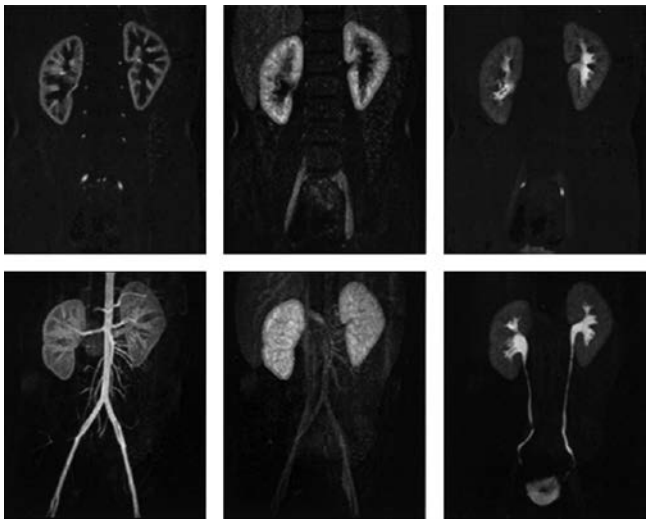


FIGURE 29.8 Following contrast administration, three distinct phases of renal enhancement can be recognized. Top row, left to right: Cortical phase, medullary phase, and excretory phase. The bottom row shows the MIPs from which images were generated.

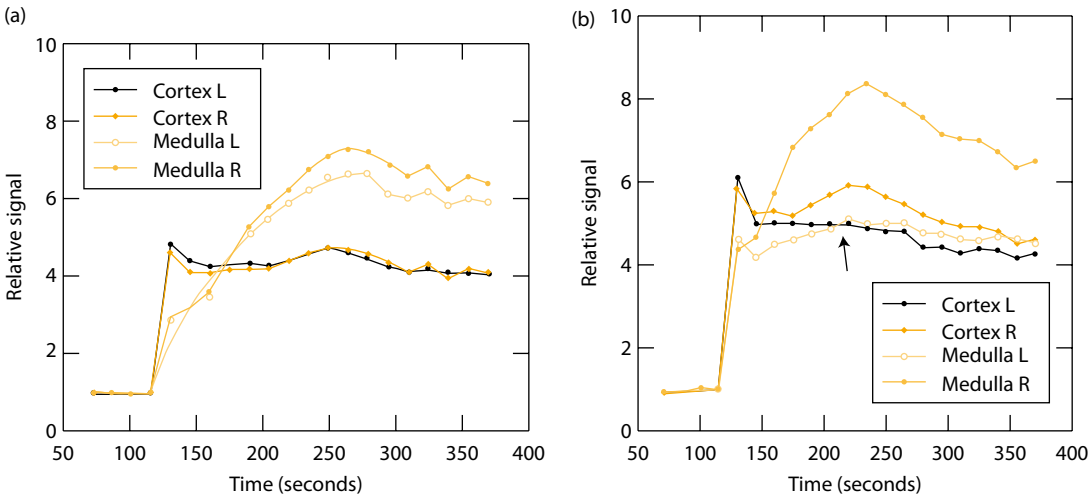


FIGURE 29.9 (a) Normal time–intensity graph. Parenchymal enhancement by MRU occurs in a predictable fashion. The CMC point (arrow) is the time at which the medulla has a higher relative signal intensity than the cortex. (b) Time–intensity graph taken from a patient with left UPJO. Delayed CMC (arrow) indicates increased intratubular pressure, which is suggestive of obstruction.

contrast, and fluid–fluid levels within the renal pelvis. With Gd-MRU, reduced enhancement and delayed excretion can be objectively quantified through the calculation of DRF and the renal transit time (RTT), which are of tantamount significance to the split renal function and $T_{1/2}$ time obtained by DRS. Using a two-compartment mathematical model, referred to as the Rutland–Patlak plot, single-kidney GFR can also be calculated with Gd-MRU.[24] This technique enables MRU-based assessment of function in patients with bilateral disease or solitary kidneys, a distinct advantage over DRS, which only provides differential information.

DRF is determined using images acquired at the time there is homogeneous enhancement within the kidney but prior to excretion of contrast into the collecting system. With 3D reconstruction, the volume of enhancing renal parenchyma is selected manually as an ROI. Vivid contrast enhancement of the renal parenchyma makes it possible to omit the collecting system and background. DRF is then calculated using the formula

$$\text{Percent renal function} = \frac{\text{Individual kidney volume}}{\text{Right kidney volume} + \text{Left kidney volume}} \times 100$$

Data published by the authors, as well as those of other clinicians, show a high correlation between DRF as determined by MRU and renal scintigraphy.[25–27]

The RTT refers to the time between the appearance of the contrast in the kidney and its appearance in the ureter (below the UPJ) and is based on 3D sequences that allow the passage of contrast to be tracked through the kidneys. Based on the RTT, drainage can be classified as normal (RTT $\leq$ 4 minutes), equivocal (4 $<$ RTT $\leq$ 8 minutes), or obstructed (RTT $>$ 8 minutes).[28] Receiver operating characteristic analysis for comparison of results by MRU and DRS shows good agreement between the modalities for the diagnosis of renal obstruction. Since the RTT includes passage of contrast through the renal pelvis, it may be falsely prolonged in cases of significantly enlarged collecting systems. As with renal versus parenchymal drainage in DRS, the caliceal transit time (CTT) (time from cortical enhancement to appearance of contrast in the calyces) eliminates the effect of a large renal pelvis on RTT. A short or symmetric CTT is highly suggestive of a nonobstructed system.[29] The unique ability of MRU to provide quantitative functional information, such as DRF and RTT, in addition to excellent anatomic characterization of the parenchyma and collecting system, makes this the most comprehensive of the currently available diagnostic studies.

Rohrschneider et al. prospectively evaluated 62 patients with static–dynamic MRU and compared the results with DRS for split function and urinary excretion, which served as the reference standard.[26] DRF, by MRU, was determined by comparing right versus left parenchymal uptake and volume, and dynamic sequences were used to generate whole-kidney ROIs, which were used to assess urinary excretion. Urinary excretion was classified similarly by MRU and DRS in 81% of the abnormal kidney–ureter units and in 100% of normal kidney units. Interestingly, in their study, MRU tended to overestimate the severity of obstruction compared with DRS. However, MRU never indicated sufficient urinary drainage when DRS indicated relevant obstruction. The higher sensitivity of Gd-MRU compared with DRS explains this finding.

One study, by Chu et al., offers limited evidence that Gd-MRU may also be more specific in the prognostication of renal deterioration than DRS.[22] In this study, eight children with unilateral hydronephrosis were evaluated by both MRU and DRS. DRS showed drainage in three hydronephrotic kidneys and poor washout in five. By contrast, Gd-MRU showed drainage in all but one of these patients. Four of the five hydronephrotic units labeled as obstructed on DRS, but that had drainage by MRU, had no evidence of worsening hydronephrosis or functional deterioration at a mean follow-up of 18 months. Furthermore, antegrade pyelography performed on two of these patients who were classified as obstructed by DRS, but not on MRU, showed

no evidence of high-grade UPJO. The one patient with an obstructive pattern by both MRU and DRS was confirmed to have significant UPJO on antegrade pyelography, and this patient subsequently underwent dismembered pyeloplasty. In a prospective study at Children's Healthcare of Atlanta comparing US, DRS, and MRU in the evaluation of hydronephrosis, MRU provided equivalent information about renal function but superior information regarding morphology in a single study without ionizing radiation.[30] Gd-MRU has also been shown to have a higher sensitivity (100% vs. 96%), positive predictive value (86% vs. 76%), negative predictive value (100% vs. 90%), and diagnostic efficiency (90% vs. 79%) than DRS.[25]

At Children's Healthcare of Atlanta, we have used Gd-MRU to evaluate more than 1500 children with hydronephrosis. MRU has been found to be particularly useful for the diagnosis and evaluation of a wide range of renal obstructive anomalies, including UPJO, megaureter, and ectopic ureters (Figure 29.10), and currently, the technique is also used to evaluate surgical results in patients pre- and postoperatively. For example, kidneys following pyeloplasty have shown statistically significant improvements in GFR (Patlak), CTT and RTT, and degree of hydronephrosis following dismembered pyeloplasty.[31] Indeed, the availability of MRU has influenced our diagnostic strategy for the evaluation of pediatric hydronephrosis. We have adapted our diagnostic algorithm to include MRU and currently use this modality in the evaluation of most patients with SFU grades 3 and 4 hydronephrosis on confirmatory sonography. Indications for surgical intervention based on Gd-MRU are more rigorous than DRS and include

- DRF of <35%–40%
- RTT of >8 minutes
- Prolonged corticomedullary crossover (CMC) times
- Decreasing GFR, as indicated by the Patlak index
- Anatomic findings

As for DRS, surgical decisions should not be based on isolated MRU criteria. Despite the advantages of MRU, there are obstacles to its widespread acceptance. First, standardized equations and values used to determine function and classify drainage have not yet been wholly agreed on. Larger studies with longer-term follow-up are still needed. Second, sedation is required for most children. Although techniques using phenobarbital or chloral hydrate have been shown to be safe, patients must be monitored throughout the study with oxygen saturation monitors. Last, there are increased costs associated with MRU and availability remains limited. Although MRU is currently more costly than renal scintigraphy, the comprehensive information obtained may justify its use, especially since it does not use ionizing radiation, and companion studies (e.g., retrograde urography) are no longer needed. Furthermore, cost and availability issues are likely to become less important in the future as use of this modality continues to increase. Indeed, over the next several years it is likely that MRU will replace renal scintigraphy in the evaluation of the pediatric urinary tract.

FIGURE 29.10 (a) A 6-year-old patient with left UPJO as seen by MRU. (b) A crossing vessel can be appreciated (arrow). (c) A 5-year-old child with bilateral nonobstructing megaureter. (d) A 9-year-old child with a right ectopic ureter, inserting below the bladder neck (asterisk), causing severe hydroureteronephrosis.

CONCLUSIONS

The accurate diagnosis and assessment of pediatric renal obstructive disorders is a principal task in pediatric urology. As a result of ongoing technologic advances, the diagnostic armamentarium available to clinicians for accomplishing this task has increased dramatically. Nevertheless, a series of radiologic studies, consisting of US, DRS, and VCUG, are still typically used to comprehensively evaluate many children. MRU has the potential to become a gold standard in the evaluation of these children. This single study, which does not require ionizing radiation, provides superior anatomic detail and, arguably, more accurate renal functional information than any other combination of studies. Cost and availability issues remain future challenges and may be the only factors preventing MRU from completely replacing renal scintigraphy.

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CHAPTER 30

Ureteropelvic Junction Obstruction and Multicystic Dysplastic Kidney: Surgical Management

Michael C. Carr and Aseem R. Shukla

INTRODUCTION

The surgical management of a kidney with obstruction at the ureteropelvic junction (UPJ) has many nuances with respect to approach, degree of invasiveness, and timing of surgery. The objective remains the same: to relieve the obstruction and thus preserve or improve the overall renal function, and maintain normal development while lessening the morbidity to the patient and yet not compromising the surgical outcome. Pyeloplasties remain among the most rewarding surgeries that we, as surgeons, perform.

The decision to recommend surgical intervention for a UPJ obstruction is based on radiographic findings that are consistent with obstruction. Debate continues as to whether a single radiographic study provides all the information necessary to make that decision. There is little argument when a mercaptoacetyltriglycine (MAG-3) lasix renogram shows markedly diminished function of the affected kidney with no apparent washout following lasix administration. These cases tend to be the exception rather than the rule. Thus, we are left with monitoring serial changes over time that indicate that there is a degree of obstruction that warrants surgical intervention. Rarely in pediatrics is a nephrostomy tube placed that allows for decompression of the kidney. If present, though, this affords antegrade assessment of the kidney. Whitaker defined obstruction in the kidney as impedance to flow such that proximal pressure must be raised to transmit the usual flow rate through it. His study involved placing catheters into the renal pelvis and bladder, infusing at 10 mL/s into the kidney, and measuring the intrapelvic pressure of the kidney. How one applies the Whitaker test to a pediatric population remains a fundamental concern. In this situation, though, a number of other tests can be performed that may be more physiologic. Performing a standard MAG-3 lasix renogram in which the nephrostomy tube is then transduced to measure intrapelvic pressure can provide physiologic data. Fung et al.[1] extrapolated the measurements of intrapelvic pressure and the decrease in pressure with time to determine a pressure decay curve. The pressure decay half-life reflects both efficient urine transport and the relative compliance and volume of the collecting system. A less compliant system with increased intrapelvic pressures could become increasingly detrimental to the overall function of that kidney.

Magnetic resonance (MR) urography has become increasingly popular as a way of providing both functional and exquisite anatomic assessment of the genitourinary system. Much like the well-tempered renogram that was described in the late 1980s, several centers have refined MR urography, both in how the study is performed and how ultimately it is interpreted. The issues now include the requirements for sedation and the overall expense of the studies. These are issues that are currently being addressed, and newer protocols are being designed to overcome these issues.[2,3]

Currently, the majority of multicystic dysplastic kidneys (MCDKs) are detected prenatally. Once detected, parents are provided with information, including natural history, postnatal evaluation, and long-term sequelae for a child with an MCDK. Subsequent prenatal imaging may be recommended by the perinatologist, which has little bearing on the ultimate outcome.

The evaluation of an infant who is known to have a prenatally detected MCDK has undergone many changes even in the past decade. The amount of imaging that was recommended previously, in most situations, is no longer necessary. Studies such as voiding cystourethrograms, renal scans, and serial ultrasounds are no longer routinely done. Nonoperative management has become the mainstay, and it has been suggested that a single postnatal ultrasound alone is all that is required.[4] In my practice, I have recommended postnatal imaging at 6–8 weeks of age. An MCDK has multiple noncommunicating cysts without the presence of renal parenchyma. The contralateral kidney is assessed for evidence of compensatory growth, in addition to documenting whether ureteral dilation is present. If the size of the MCDK is initially greater than 5 cm, the involution rate of this kidney will be less than if it is less than 5 cm.[5] A subsequent renal and bladder ultrasound done at 1 year of age is beneficial to determine whether involution has occurred or whether the kidney has actually become larger over time. Since the overwhelming majority of kidneys do

show involution, no further urologic follow-up is needed.[4] If the kidney has become larger and the infant is now 1 year of age, open or laparoscopic nephrectomy can be offered to the family. A review of data from the Children's Hospital of Philadelphia between July 2007 and June 2012 showed that a total of 75 laparoscopic or open nephrectomies were performed. Twenty-one of these patients during this time interval had an MCDK. Thus, less than one nephrectomy for an MCDK per surgeon per year was being done at a large tertiary referral center, indicating that nonoperative management has become the norm.

Once a surgeon diagnoses a UPJ obstruction, prompt intervention is necessary to relieve the obstruction, provide for appropriate drainage, and reduce the intrapelvic pressure and stasis that contributes to progressive renal damage. This is particularly important in the neonatal period in order to maximize functional renal development and increase the ultimate number of perfused and filtering nephrons.[6] In those kidneys where the differential function is less than 10%, a temporary nephrostomy tube or double-J stent placement may allow for separating kidneys with recoverable function from those with irreversible damage.[7,8] Renal biopsies may also be performed to identify diffuse glomerulosclerosis that would indicate little chance for improved postpyeloplasty function.[9] No test, though, is reliable to predict renal recoverability.

TECHNICAL POINTS OF OPEN PYELOPLASTY OR SIMPLE NEPHRECTOMY

The approach for a pyeloplasty or nephrectomy has migrated from an open approach to a minimally invasive one, utilizing laparoscopic techniques. A standard flank, anterior subcostal, or posterior lumbotomy skin incision may be used to expose the kidney for pyeloplasty or nephrectomy, when approached in an open fashion. I recommend the minimally invasive approach with mobilization of the kidney for older patients. In the child or infant, however, where the anterior and posterior muscles are less well developed, most pediatric urologists favor an anterior extraperitoneal approach or a dorsal lumbotomy incision. The anterior extraperitoneal approach is performed as follows: A subcostal incision is made after the patient is placed supine with a roll placed transversely beneath the patient to elevate the flank (Figure 30.1). An incision is made from the edge of the rectus muscle to just below the tip of the 12th rib. An intraoperative retrograde pyelogram allows one to identify precisely the position of the UPJ and aide in the placement of the incision. Each muscle layer encountered is split in the direction of the muscle fibers until the surgeon defines Gerota's fascia by sweeping the peritoneum medially. The fascia is then incised posterior to the lateral aspect of the kidney. The renal pelvis is identified by medial retraction of the peritoneum and lateral traction of the kidney. If the pelvis is dilated, an angiocath can be inserted to decompress the pelvis and facilitate identification of the UPJ.

Alternatively, the lumbotomy approach in infants and younger children can be employed. A transverse skin incision, which follows Langer's lines to avoid postoperative spreading of the scar, is made with subsequent mobilization of the skin before a vertical incision through the lumbodorsal fascia. This allows the surgeon direct access to the renal pelvis. The kidney is then mobilized to gain access to the renal pelvis (Figure 30.2).

FIGURE 30.1 Appropriate positioning of patient for left anterior subcostal incision. The tips of 11th and 12th ribs have been outlined and 4 cm incision has been drawn.

FIGURE 30.2 Appropriate positioning of patient for left posterior lumbotomy approach. A curvilinear incision is marked, which can be used, or a transverse skin incision can be employed.

The closure is in one layer, which shortens operative time. In the case of bilateral UPJ obstruction, the surgeon may approach both sides without repositioning the patient. The lumbotomy approach is contraindicated if one is dealing with an incompletely rotated anterior renal pelvis. If there is an anomaly of position, the surgeon must locate the position of the UPJ before planning the incision. If the obstructed pelvis is mostly intrarenal, small or high, then a lumbotomy approach may be more difficult. In addition, muscular patients with a steep angle between the spine and the 12th rib may also present difficulties with exposure of a small or high pelvis. If caught unprepared with a particularly superior renal pelvis, the 12th rib can be disarticulated and rotated cranially to improve exposure, but in these cases, an anterior approach is preferable.

The flank approach is another option. The child is placed over the kidney rest in a flank position; the kidney rest is elevated and the operating room table is flexed. The incision is made anterior to the tip of the 12th rib, or if necessary, a supracostal 12th rib incision is made. Both the external oblique and latissimus dorsi muscles are divided. Next, the internal oblique and serratus posterior inferior muscle are divided. A transversalis muscle is often thin and can be separated with digital dissection. The peritoneum is identified and retracted medially. Gerota's fascia is then encountered and opened longitudinally to gain exposure to the perinephric space. Following identification of the renal pelvis and the ureter, the pyeloplasty is performed.

In a redo pyeloplasty, the anterior transperitoneal approach is preferred. Once the colon is reflected, the anatomy can be rapidly identified and damage to the ureter, renal pelvis, or renal vessels can be avoided by exploring a scarred retroperitoneum through a posterior approach to the kidney.

In the situation of a simple nephrectomy to remove an MCDK, any of the above-described approaches are applicable. If a small incision is utilized, decompression of the largest cysts will optimize exposure and allow for improved visualization of the renal hilum. Invariably, the renal vasculature is atretic in most situations, but careful dissection will avoid meddlesome bleeding. Bipolar cautery can be advantageous for such a dissection.

SURGICAL REPAIR

The successful pyeloplasty depends on a carefully designed anastomosis with care taken to ensure that the ureter and pelvis will lie in a normal anatomic position at the completion of the pyeloplasty. In the past, surgeons have described a series of various techniques to repair the UPJ, with open approaches being divided into three main groups: the flap type, the incisional-intubated type, and the dismembered type. The incisional techniques included incision through the strictured area with healing over a stent. This approach is no longer used with open repair. The older flap techniques to maintain the continuity of the ureter and pelvis included the Foley Y-V plasty and the Culp spiral flap. The Foley operation was designed for the correction of UPJ with a high ureteral insertion (Figure 30.3).[10] This technique cannot be used in conjunction with transposition of a lower-pole vessel, nor does it allow for any reduction of the renal pelvis. If this redundant pelvis remains at the completion of the pyeloplasty, then a fixed kink with resultant obstruction may persist. Culp and DeWeerd's spiral flap is created from the renal pelvis, which is then used to repair the defect at the UPJ. Such a flap is able to bridge the gap between the pelvis and healthy ureter over a distance of several centimeters (Figure 30.4).[11] Scardino and Prince[12] used a vertical flap that was designed in a situation of a dependent UPJ with a large, square-shaped extrarenal pelvis (Figure 30.5).[13]

The approach of dismembering the ureter was borne out of necessity in the repair of a retrocaval ureter (Figure 30.6).[14] This technique was slow to gain popularity because of the reluctance of surgeons to sever the apparent neural continuity between the pelvis and ureter. Experimental work demonstrated that the arborization of blood vessels in the renal pelvis would ensure appropriate healing even with dismembering. Despite the theoretical risk of poor coordination of peristalsis across the incised and reconstructed UPJ, the reconstructed pelvis empties well following successful dismembered pyeloplasty.

The renal pelvis and upper ureter must be carefully handled to maintain the integrity of the blood supply. The tissues surrounding the ureter should not be trimmed or separated from the ureter. Placement of several traction

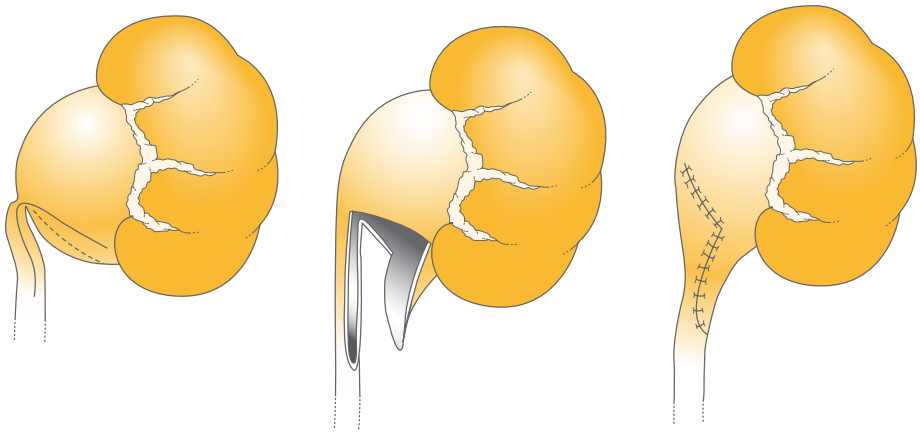

FIGURE 30.3 Foley Y-V plasty.

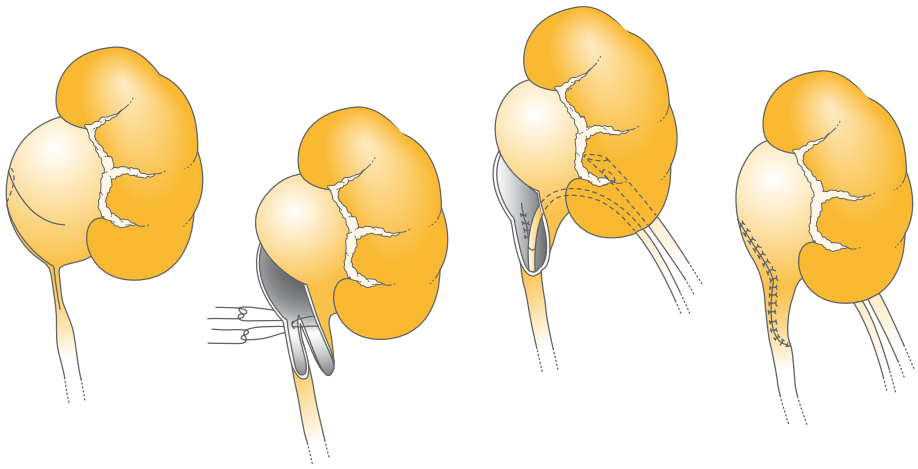

FIGURE 30.4 Culp–DeWeerd spiral flap ureteropelvioplasty.

sutures in the renal pelvis and the anterior aspect of the ureter facilitates this dissection and minimizes the handling of the tissues. We then open the ureter opposite the traction suture distally into the healthy tissue just below the poorly peristaltic segment. A fine pair of forceps will open the ureteral lumen as the ureter is divided using a straight pair of Pott's scissors. The forceps should spring apart once the scissors meet the healthy ureter distal to the obstructing segment. Bleeding from the cut edge of the urothelium, which is usually diminished in the region of the obstructed segment, will be brisk when the normal urothelium is opened distal to the obstruction. As long as the renal pelvis is not reconstructed before examination of the ureter, if the aperistaltic segment is unusually long, a flap can be fashioned from the pelvis to help bridge a discontinuity between the renal pelvis and distal ureter that may be

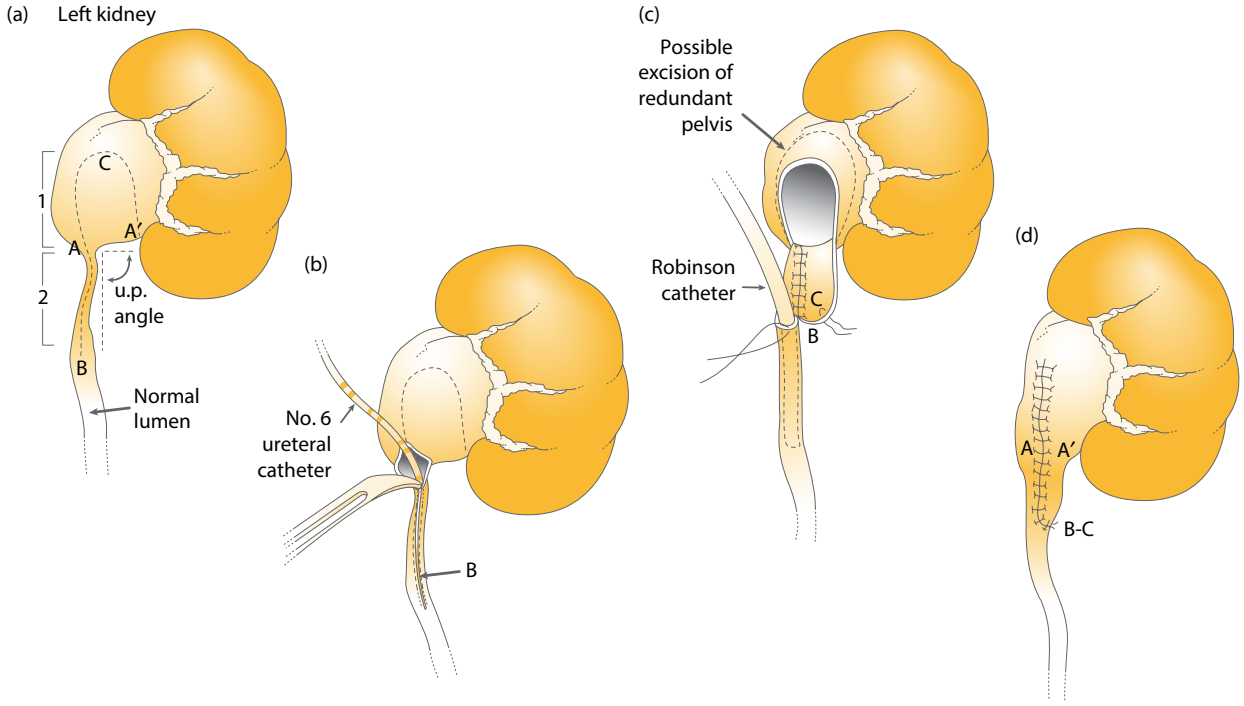

FIGURE 30.5 Scardino–Prince vertical flap pyeloureteroplasty. (a) The length of the pelvic flap (1) should adequately traverse the segment of ureteral obstruction (2). (b) A pyelotomy incision is made in the lower pelvis along the medial border of the proposed pelvic flap incision. A 6 French catheter is used to cannulate the ureter and the tip of a #12 blade is inserted into the catheter. The catheter acts as a guide to make a clean, precise ureterotomy incision. (c) A 5-0 prolene (Ethicon) suture is placed within the ureteral wall at the lower angle of the ureterotomy. A rounded pelvic flap is fashioned, and a second traction suture is placed in the tip of the flap. A 7-0 maxon (Davis–Geck) suture or comparable suture is used to suture the medial margin of the flap to the lateral ureteral margin. The mucosa margins should be identified for accurate approximation. (d) The tip of the flap (C) is carefully sutured into the lower angle of the ureterostomy (B). Any redundant pelvis may be excised and the anterior margins reapproximated (B and C, A and A′).

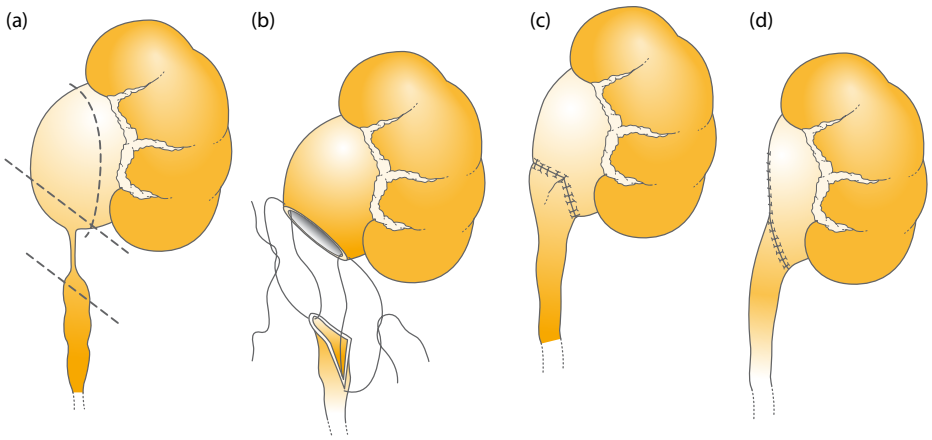

FIGURE 30.6 Anderson–Hynes dismembered pyeloplasty. (a) Two options: The pelvis may be reduced in size or not. (b and c) Anastomosis alone is performed. (d) A reduction pyeloplasty is included.

created with removal of a long ureteral segment. A ventral rotational flap from the lower portion of the pelvis can be used to bridge a gap of 2–3 cm, more if the kidney is mobilized. Reduction of the renal pelvis is completed before beginning the anastomosis. Prior to the anastomosis, the interior of the renal pelvis should be inspected to precisely identify the anatomy of the renal pelvis and its relationship to the lower-pole infundibula. In some cases, a very dilated pelvis may be associated with dilated, extrarenal infundibula. In these cases, it is possible to unknowingly create the ureteral pelvic anastomosis in such a manner that the lower-pole infundibulum, rather than the renal pelvis, is anastomosed to the ureter. If this occurs, the upper portions of the collecting system will be bypassed and will fail to drain. If an infundibulum is divided, a Heineke–Mikulicz advancement can satisfactorily prevent this complication. In the face of aberrant lower-pole vessels that contribute to the UPJ obstruction, the appropriate repair is to divide the ureter below the UPJ and perform a standard dismembered pyeloplasty with reconstruction of the UPJ anterior to the offending vessel or vessels.

TISSUE HANDLING, SUTURES, AND STENTING

The judicious use of traction sutures allows for minimal handling of the pelvis and ureter. The more the surgeon handles (or mishandles) the tissue, the more postoperative edema that will result. Without the use of urinary diversion, attention to atraumatic handling of the tissues becomes critical. In mobilizing the pelvis, similar care is required. An avascular plane is usually located outside the intrinsic blood supply of the pelvis, unless there has been significant preoperative infection or extravasation of urine around the kidney that makes mobilization of the pelvis more difficult.

Monofilament absorbable suture is preferable for performing a dismembered pyeloplasty. I prefer 7-0 Maxon suture (Davis–Geck) for the majority of children, regardless of age. Construction of the anastomosis begins at the apex, with meticulous placement of sutures, allowing for eversion of the skin edges and a watertight anastomosis. Some surgeons prefer interrupted sutures to prevent reduction of the anastomotic diameter. Others employ a running closure. Before completing the anastomosis, it is helpful to place a small angiocath or feeding tube in the renal pelvis to irrigate the reconstructed pelvis free from clotted blood.

Antegrade placement of a double-J stent is fraught with hazard, particularly in infants. It is safe for the surgeon to place a small feeding tube several centimeters below the anastomosis. If the tube is advanced to or through the intramural portion of the ureter, however, the catheter may traumatize the ureterovesical junction and raise a mucosal flap that can lead to a permanent obstruction requiring redo surgery.[15] Either preoperative retrograde pyelography or antegrade visualization of the ureter with placement of the catheter over a wire under fluoroscopic guidance may help prevent this complication.[16]

Surgeons continue to debate the use of internal stenting versus the use of nephrostomy tubes. A routine dismembered pyeloplasty with minimal handling of the tissues may not warrant the placement of either nephrostomy tube or internal stent. On the other hand, infant pyeloplasties may benefit from internal stenting, particularly if the retrograde pyelogram shows evidence of a "beaded ureter" appearance. This signifies peristaltic abnormalities of the immature, proximal ureter that benefit from internal stenting.

Advances in instrumentation, sutures, and technique have enabled the construction of such a satisfactory anastomosis that even if transient leakage from the anastomosis occurs after surgery, a very satisfactory outcome is likely. A Penrose drain left in the proximity of the anastomosis to ensure that a perinephric urinoma does not occur is required in these cases. If the child has persistent drainage from the Penrose, he or she can be discharged from the hospital with the drain still in place. For the most part, however, drainage gradually ceases after the first few days following surgery, and then the Penrose drain can be safely removed.

The routine use of a nephrostomy tube is a very safe approach with few complications.[17] Selective use of a nephrostomy tube, particularly in the child with a solitary or poorly functioning kidney or a very small infant where the

ureter may not be nearly as robust as in a toddler, is usually preferable. The nephrostomy tube not only prevents high renal pelvic pressures if there is transient edema at the anastomosis, but also provides access for radiographic studies before removal of the tube.

In a redo pyeloplasty, scarred urothelial tissue may result in greater difficulty when performing a watertight anastomosis. For this reason, a nephrostomy tube along with a small silastic stent across the anastomosis for 3–5 days following surgery is beneficial. This splenting of the repair, in addition to the nephrostomy tube, allows one to remove the stent before the nephrostomy tube so that a subsequent nephrostogram can be performed to ensure that the anastomosis is patent before removal of the tube.

ROBOTIC-ASSISTED LAPAROSCOPIC PYELOPLASTY

Robot-assisted laparoscopy, using the only currently available platform, da Vinci® (Intuitive Surgical Inc., Mountainview, California), has greatly augmented the reconstructive utility of laparoscopy in children. The system overcomes the visual, spatial, maneuverability, and ergonomic limitations of traditional pediatric laparoscopy, and recent studies confirm the efficacy, safety, and applicability of robot-assisted laparoscopy in children. The da Vinci system allows the "transitioning" surgeon to attempt complex laparoscopic surgery with its inherent advantages: three-dimensional visualization (now in high definition), articulating instruments with greater degrees of freedom, and dampening of tremor. The robot is an "enslaved device" under the control of the surgeon that has electromechanical arms equipped with sensors and actuators that move precisely under the control of a surgeon seated at a remote console. The most obvious advantage of pediatric robotic surgery, then, is manifest in its facilitation of intracorporeal suturing.

Extensive experience with the robotic-assisted laparoscopic pyeloplasty (RALP) has now been documented by multiple institutions.[18–22] Longer-term experience seems to confirm the viability of the repair, and reduced morbidity and hospital stay in older patients. Definitive data confirming that even small infants may safely undergo RALP are emerging,[4] although postoperative outcome advantages measured in metrics of length of hospitalization, narcotic analgesic use, intraoperative time, and cosmesis are lacking.

TECHNIQUE

All children complete a routine outpatient bowel preparation with oral polyethylene glycol the night before RALP. Immediately after a broad-spectrum intravenous antibiotic is administered, general anesthesia is induced and the child is positioned in a low dorsal lithotomy position. Cystoscopy and retrograde ureterography are performed to characterize the ureteral defect. We prefer to place a double-J stent in advance with its tether secured to the ipsilateral groin. There are several alternatives for stenting of the ureter, and opinions diverge as to putative advantages. Alternatives include the placement of a 5 French open-ended catheter up to the midureter and then securing it to the Foley catheter. A guidewire can then be inserted under direct vision after dismembering of the ureter for retrograde stent placement. Antegrade placement of a guidewire into the distal ureter via an angiocath sheath percutaneously placed is also a popular option.

After a Foley catheter is inserted, the child is repositioned and secured in a mild lateral decubitus position, exposing the affected side. We prefer to position and carefully secure the child's contralateral flank as close to the operating table edge as possible. We prefer to secure the ipsilateral arm along the patient's side, especially in children where positioning that arm over the face can be difficult due to extremity length. This positioning allows maximal subsequent movement of the camera in an inferior direction to visualize the ipsilateral side intracorporeally. An infraumbilical 12 mm camera port is placed using a modified Hasson technique to obtain the pneumoperitoneum. A 30° down-looking camera is introduced into the peritoneal cavity. Under direct vision, two 5 mm instrument ports are placed in the midclavicular line triangulating approximately 7 cm apart from the umbilical port and 10 cm apart from each other.

We utilize the 5 mm ports in children and have done so for our last 50 robotic cases, fully aware that this accommodation requires the surgeon to compromise on the superior instrumentation available with the more commonly available 7 mm port system. Most apparent is the lack of a 5 mm robotic scissor that also provides monopolar diathermy. Still, the enhanced cosmesis and easier closure for 5 mm instrumentation has encouraged us to transition to the smaller port size. In our early experience, we preferred placement of a fourth 5 mm port for insertion of an assistant port for laparoscopic retraction and passing and cutting of sutures. Over the last 6 years, we have obviated the need for a separate assistant port by passing sutures and handheld instruments into the peritoneal cavity via the 5 mm robotic instrument ports.

This three-port template is rotated about the umbilicus in a patient-specific manner based on the location of the ureteral defect. The patient is then maximally rotated in the direction contralateral to the ureteral lesion side after careful securing of the patient. The da Vinci robot system is then docked in the standard fashion with the robotic patient cart advanced to a position equidistant from two 5 mm ports. The 5 mm ports are placed such that the camera arm and instrument arms triangulate towards the location of the ureteral lesion. In advancing the camera arm to dock to the camera port, care is taken to ensure that the specifically demarcated "sweet spot" of the camera arm is preserved.

After mobilization of the colon and incision of Gerota's fascia, the ureteral defect is meticulously isolated with minimal manipulation and potential devascularization. A short proximal ureteral obstruction can readily be isolated via a transmesenteric approach, especially on the left side, limiting the need for medial retraction of the descending colon. For distal ureteral lesions or right-sided lesions, the colon may be mobilized. Our preference is to identify normal ureter distally, even as it passes over the bifurcation of the iliac vessels if necessary, and then following the ureter proximally until the site of the obstructive lesion is identified.

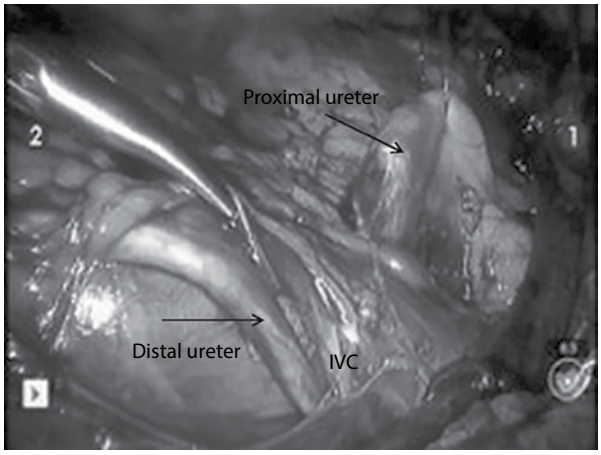

FIGURE 30.7 Intraoperative view of right retrocaval ureter. The robotic-assisted dissector is seen holding the proximal right ureter that then disappears behind the IVC.

The ureter is then transected sharply and spatulated ventrally and dorsally as needed. Ureteral manipulation to transpose over a potentially compressive vascular structure—as with a lower-pole renal crossing vessel or inferior vena cava (IVC)—is then accomplished. In a case with a retrocaval ureter (Figure 30.7), the proximal ureter is sharply divided lateral to the IVC and the retrocaval portion of the ureter is freed medially and transposed anterior to the IVC (Figure 30.8). The proximal ureter is stabilized with a 2-0 polypropylene hitch stitch to facilitate reconstruction. A tension-free watertight ureteroureterostomy is then fashioned over the double-J stent using separate posterior and anterior wall closures of running 6-0 polydioxane. We do not hesitate to use 5-0 polydiaxone for older children. We utilize a running anastomosis that begins at the vertex of the spatulation and proceeds superiorly on the medial and lateral walls of the ureter. Gerota's fascia is reapproximated with interrupted 6-0 polydioxane stitches. A 10 French round bulb suction drain is positioned over the renal fossa via the inferior instrument port. The umbilical port site fascia is closed using 2-0 polyglactin suture. All port sites are then closed using subcuticular 5-0 absorbable monofilament. The Foley catheter and Jackson–Pratt drain are removed the morning after surgery. Patients are routinely discharged to home the day after surgery. The double-J stent is removed 10 days postoperatively, either at home or in the clinic, via the externalized tether. Patients are followed up at 1 month postoperatively with a renal ultrasound to evaluate for changes in hydronephrosis or as per the institutional routine for standard open pyeloplasty.

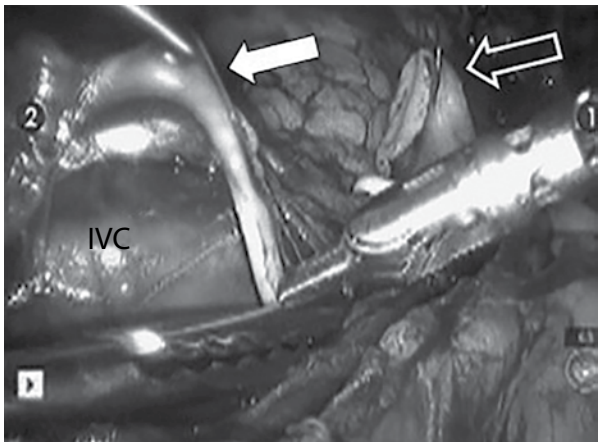

FIGURE 30.8 Intraoperative photograph of the transected proximal ureter (open arrow), which is lateral and anterior to the IVC, being stabilized with an abdominal wall hitch stitch. It will be sutured to the distal ureter (solid arrow) after being transposed anterior to the IVC.

UPJ OBSTRUCTION IN A DUPLEX KIDNEY

A UPJ obstruction can occur in a duplex kidney. Although the obstruction can occur in either the upper or the lower pole, because the lower pole is nearly always dominant and associated with the renal pelvis, in practice the UPJ obstruction is nearly always encountered in the lower-pole system. When this occurs, hydronephrosis is noted in the lower pole of a kidney on ultrasound, or a diuretic renogram shows a small, nonobstructed upper-pole segment (Figure 30.9). The anatomy of the duplication of the ureter dictates the type of procedure required. If the ureter is incompletely bifid and there is a long lower-pole ureteral segment, then a standard dismembered pyeloplasty is appropriate. However, more commonly, a high bifurcation of the ureter is present and the segment of the lower-pole ureter distal to the obstruction may not be long enough to permit direct ureteropyelostomy. In this situation, the renal pelvis is anastomosed to the side of the ureter (Figure 30.10). The lower-pole ureter may be opened with an incision that runs through the bifurcation with the upper-pole ureter. The anastomosis is the same as for a single system kidney, except that an apex is present at either end of the lower-pole pelvis. Meticulous care with the suture placement at the apices is important because the anastomosis will be narrow at these two points. If the anastomotic sutures are placed in discordant positions, the lumen at either apex will be narrowed, resulting in surgical failure.

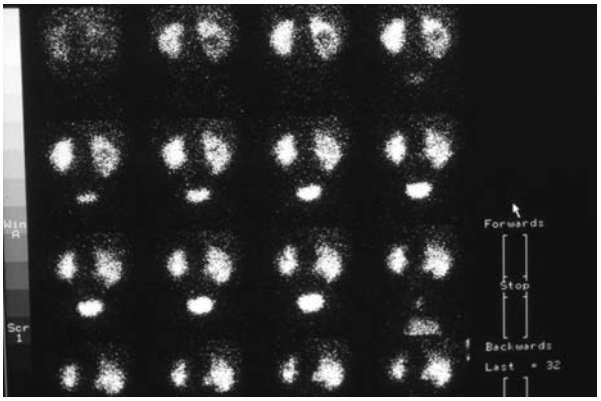

FIGURE 30.9 MAG-3 lasix renogram demonstrating normal right upper-pole perfusion and excretion with delayed uptake and excretion to the lower pole, consistent with lower-pole UPJ obstruction.

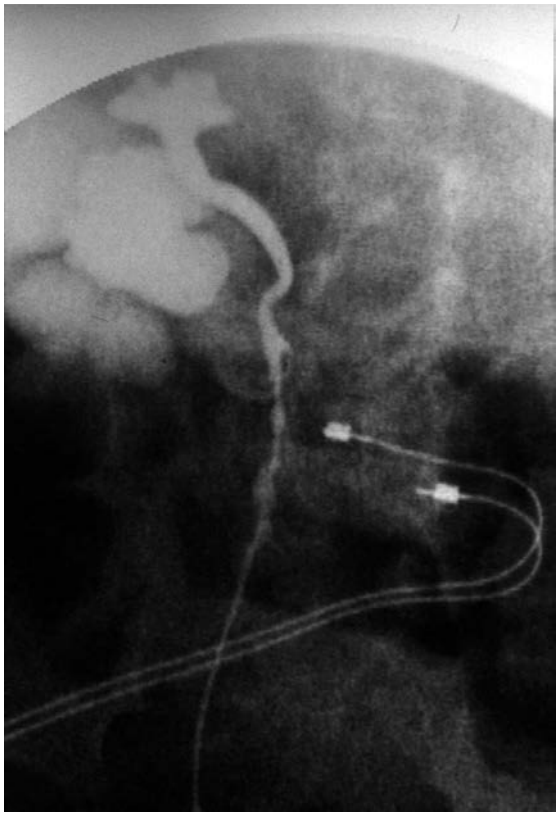

FIGURE 30.10 Anatomy of right lower-pole UPJ obstruction with atretic lower-pole ureter. An end-to-side anastomosis between the lower-pole renal pelvis and upper-pole ureter is favored.

URETEROCALICOSTOMY

In redo surgery, or in cases where the pelvis is intrarenal, or the relative length of the obstructed ureteral segment to the renal pelvis is unusually long, or if there is an unusually small intrarenal pelvis, the proximal ureter distal to the obstruction may be anastomosed to a dependent lower-pole calyx instead of to the renal pelvis. Success depends on amputation of an adequate portion of the renal parenchyma in order to facilitate the anastomosis between the calyx and the ureter. This procedure is therefore best suited for kidneys with a large, dilated lower-pole calyx with overlying parenchymal thinning. The calyx must be partially mobilized to create a tension-free urothelium-to-urothelium anastomosis (Figure 30.11). There should be no remaining renal cortex at or below the level of the repair. Redundant renal capsule, omentum, or perinephric fat can then be used to cover the repair to minimize postoperative scarring. I recommend stenting of the anastomosis with a double-pigtail stent or nephroureteral stent, in addition to a Penrose drain.[23]

A robotic-assisted laparoscopic approach to the ureterocalicostomy is also feasible.[24] In cases where the initial pyeloplasty was completed from a retroperitoneal, flank approach, there may even be putative advantages to laparoscopy as an intraperitoneal access enters a potentially undisturbed tissue plane.

Prestenting of the ureter may be preferable in these cases to easily identify the proximal ureter distal to the scarred operative field. After docking the robot in the aforementioned manner as with a standard pyeloplasty—triangulating ports toward the region of the UPJ—the ureter is transected as proximally as possible. The ureter is spatulated generously to ensure normal, well-vascularized ureteral mucosa is visible. The lower pole of the kidney is then identified, and the dependent lower pole is amputated using the 8 mm robotic shears connected to monopolar diathermy. We utilize 5-0 polydioxane suture material to then perform a mucosa-to-mucosa anastomosis of the proximal ureter to the lower-pole calyx in an interrupted and continuous fashion. No attempt is typically made to cover the anastomosis with friable renal capsular material, but omentum or perinephric fat may be affixed over the repair site. The stent is then removed 4 weeks postoperatively.

ENDOPYELOTOMY

A purely endoscopic approach to a UPJ obstruction can arguably be considered the most minimally invasive surgical treatment. Surgical techniques include antegrade and retrograde approaches that are guided fluoroscopically, and incisions performed with direct ureteroscopic visualization utilizing holmium laser or electrosurgical incision. The advent of the Accucise® endopyelotomy catheter, and success in adults, led to clinical trials in the pediatric population with UPJ obstruction.

The procedure is performed after fluoroscopically guided placement of a guidewire across the UPJ. The Accucise cutting balloon catheter is introduced over the wire in an antegrade or retrograde fashion, depending on the preferred access percutaneously or cystoscopically. The balloon is inflated, and once a narrowing within the midpoint of the balloon catheter is noted, the Accucise blade is activated with cutting current positioned laterally. A double-J stent is typically placed and removed after 3–8 weeks. When ureteroscopy is preferred, a holmium laser with a right-angle electrode is focused laterally at the UPJ until periureteral fat is visualized.[25]

While preliminary reports indicated success in the pediatric population ranging from 70% to 88%,[26,27] Kim et al.[28] recently published a 25-year experience with pediatric endopyelotomy. The long-term success for primary endopyelotomy—regardless of approach or whether performed with Accucise or with laser—was only 65%. Consistent with previous studies, the authors found that higher grades of hydronephrosis significantly impaired renal function and the presence of a crossing lower-pole vessel was associated with failure in their cohort.[28,29] The results were more encouraging, however, for secondary endopyelotomy after previously failed pyeloplasty. The success rate for this cohort of 31 patients was 94% at a median 5 years of follow-up, which compares favorably to open approaches, and confirms a continued role for the endoscopic option in select patients without a crossing vessel and retained renal function.

OUTCOME

Adherence to sound surgical principles, minimal handling of the ureter at the time of the repair, and judicious use of internal stenting or nephrostomy tube drainage all may

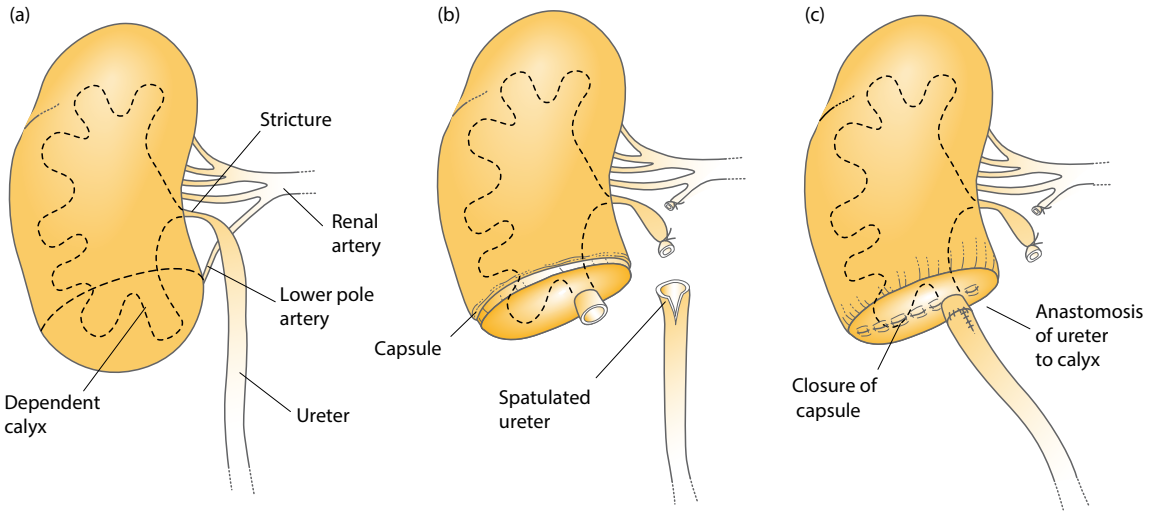

FIGURE 30.11 Ureterocalicostomy of a kidney with an intrarenal pelvis and preserved lower-pole parenchyma. (a) The lower-pole arterial supply is ligated. (b) The lower pole is resected exposing dependent calyx. (c) Anastomosis of the ureter to the calyx is accomplished without tension.

help to ensure a successful outcome. I have found that bipolar cautery is useful, particularly around the renal hilum, where the blood supply may be suspect.

Postoperative imaging of the kidney depends on whether a nephrostomy tube or an internal double-J stent has been used. A nephrostogram performed 10–14 days after surgery allows for visualization of the anastomosis. If a double pigtail ureteral stent is left indwelling, it is removed 2–6 weeks after the initial procedure. A renal ultrasound is obtained 6–8 weeks after pyeloplasty or following stent removal to ensure that the hydronephrosis (pelvicaliectasis) is improving. An overall decrease in the degree of pelvicaliectasis over time is a good indication that the obstruction has been relieved. Longer-term imaging 1 year after surgery will provide one with a good idea of whether pelvicaliectasis persists. Imaging beyond this point is debatable in an asymptomatic patient, and functional studies are generally reserved for situations in which there was a marked disparity in overall renal function prior to surgery (e.g., differential function of 70%/30% prior to pyeloplasty) or if one is not happy with the degree of persistent pelvicaliectasis that exists after surgery and there is concern that ongoing obstruction exists. Modern open repairs can be performed with an overall success rate exceeding 97%.[30]

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CHAPTER 31

Laparoscopic and Robotic Nephrectomy and Pyeloplasty

Daniel Avery and Thomas Lendvay

INTRODUCTION

Beginning in the 1990s, minimally invasive surgical techniques were being applied to primarily adult and some pediatric patients, the impetus being a reduction in incision sizes, less perioperative pain, scar reduction, and a decreased convalescence. Laparoscopic surgery was initially adopted for extirpative operations. Clayman et al. described the first laparoscopic nephrectomy in 1991.[1] This was translated into the pediatric population and expanded to include many renal surgeries, such as heminephrectomy, partial nephrectomy, nephroureterectomy, cyst excision, and pyeloplasty.[2–4] The type of approach was also broadened from transperitoneal to retroperitoneal.[5] Given the steep learning curve, limited degrees of freedom for the instruments, and two-dimensional (2D) imaging of the operative field, laparoscopic surgery in pediatrics had a slow adoption rate. This was particularly true for reconstructive techniques, such as pyeloplasty, due to the difficulty of intracorporeal suturing.[6]

Robotic-assisted laparoscopic surgery improved on pure laparoscopy with three-dimensional (3D) vision, motion scaling, tremor abatement, and increased degrees of freedom of the instruments, but the high cost of equipment and relatively larger trocar sizes led to a delayed adoption in the pediatric patient population. There was also concern about the large physical size of the robot limiting anesthesia access to the patient and the inadequate size of the operative field to maneuver the instruments in pediatric patients.[7] An elegant study by Thakre et al. showed that there is a minimum size of the working operative field for the surgical robot—130 mL—about the size of a 2-year-old's bladder.[8] The rapid adoption of surgical-assisted laparoscopy in the adult population, the development of smaller instrument and camera sizes, the ease of intracorporeal suturing, and the increase in safety literature in children have led to a recent increase in the adoption of the surgical robotic platform in pediatric cases. Robotic-assisted laparoscopic urologic procedures have expanded to include nephrectomies, partial nephrectomies, dismembered pyeloplasties, ureteroureterostomies, ureteral reimplantations, varicocelectomies, orchiopexies, appendicovesicostomies, antegrade continence enema channels, urachal cyst removals, bladder neck reconstructions, and bladder augmentations.[9–17] We will highlight the most common renal procedures performed using the robot in children.

NEPHRECTOMY AND HEMINEPHRECTOMY

Indications

Nephrectomy and heminephrectomy are generally employed to remove poorly functioning or nonfunctioning renal moieties due to vesicoureteral reflux, obstruction, or ectopic insertion of the ureter. When the decision is made to remove the offensive moiety, special considerations must be made, such as ensuring the preservation of the retained functional renal moiety and ureter if possible. Nonfunctioning upper- or lower-pole renal moieties tend to have hypoplastic renal vasculature; however, some have hila that require suture ligation. Laparoscopic surgery provides excellent visualization of the renal hilum, and furthermore, a robotic-assisted approach allows for easy suture ligation. In addition, transposition under the "good" renal hilum of the typically dilated upper-pole ureter in the case of a duplex system with a dysplastic upper-pole renal moiety is facilitated by the dexterous capabilities of the robot.

Pediatric patients also undergo total nephrectomy for multicystic dysplastic nonfunctioning kidneys and renal tumors, or prior to renal transplantation if severe hypertension, nephrotic syndrome, or hemolytic uremic syndrome exists. The setups for heminephrectomy and nephrectomy are the same. The key considerations revolve around control and division of the renal hilum. The dexterity of the robotic end effectors facilitates precise dissection of the perihilar lymphatics without injury to the renal vasculature. We prefer to use either titanium clips or suture ligation of the renal vessels. The monopolar shears, Ligasure™ bipolar, or ultrasonic devices are then used to divide the vessels and complete the upper-pole perirenal dissection.

Renal Access

The traditional access for open renal surgery is usually through a flank or subcostal incision. With the introduction of laparoscopy, the access became the classic transperitoneal triangulated port placement with an umbilical access usually for the camera, and two or three working ports—one in the midline subxiphoid, one along the

ipsilateral midaxillary line at or below the level of the umbilicus, and possibly an assist port between the camera and either working port. Retroperitoneal access is also possible, and surgeon comfort should be the driver for this decision.

The setup for a robot-assisted laparoscopic nephrectomy is a modification of the pure laparoscopic approach. We will describe the setup and note differences between the two modalities where necessary. Furthermore, the positioning, port placement, and procedure are essentially the same for nephrectomy and heminephrectomy. Since heminephrectomy is technically more intricate, it is described in detail. For nephrectomy, since there is no healthy moiety the entire hilum is dissected and ligated, as is the ureter if necessary.

Transperitoneal Access

For renal access, patient positioning involves a modified flank orientation with the ipsilateral side up. We usually use gel rolls or rolled-up blankets to support the roughly 30° patient plane (Figure 31.1). This low flank position precludes the need for axillary rolls to prevent brachial plexopathies and avoids the need to raise the ipsilateral arm over the patient's chest. We support the ipsilateral arm at the shoulder with additional gel rolls. For a robotic approach in children less than 2 years of age, the robot arms may collide with the table (especially with older iterations of the da Vinci®) unless the child is raised up, so we create a blanket stage roughly 4–6 inches off the table (Figure 31.2). The patient must be brought close to the contralateral side of the table's edge; however, we leave enough room for the contralateral arm to lie next to the child, as opposed to using perpendicular arm boards. Both arms must be appropriately padded and maintained in a position of function with foam or tiny gel rolls supporting a mild flexion of the elbow and fingers.

For right-sided upper-pole heminephrectomies, liver retraction may be required. Ensuring that the contralateral subcostal margin is within the sterile field for additional retraction port access is imperative. We use an additional

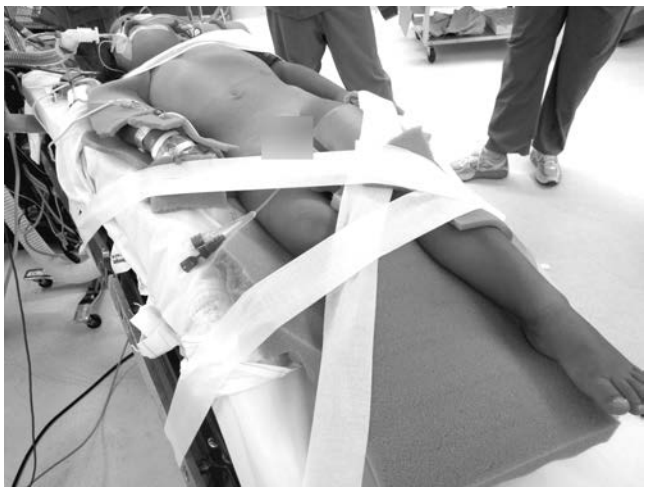

FIGURE 31.1 Patient is rolled to mild 30° flank with a straight arm at the side position.

FIGURE 31.2 Infant positioning for left pyeloplasty. Patient is bumped up on a padded stage composed of blankets and foam to avoid robotic arm collisions with the bed.

3–5 mm disposable radially dilating port below the left costal margin to insert a locking reusable grasper, which suspends the right lobe of the liver cephalad by clamping the grasper to the lateral superior peritoneum below the diaphragm. In addition, the child should be placed in a slightly steeper flank position, anticipating complete reflection of the colon. This degree of flanking may require an axillary role to be placed to prevent brachial plexopathies, especially in heavier older children. Maintaining extremity position of function and appropriate padding is necessary. Once the patient is secured to the table after mild flexion of the bed, the patient's position should be tested for stability by rotating the bed from the "patient-flat" position to the greatest degree of lateral rotation that is expected to ensure that the patient does not move. A urinary catheter is placed to decompress the bladder.

We place our superior working port in the midline subxiphoid under direct vision and cheat toward the ipsilateral side of the falciform ligament so as not to create potential bleeding from the ligament, which in infants may still have a slight degree of vessel patency (Video 31.1). The inferior port is placed either on the ipsilateral midaxillary line or even in the midline infraumbilically, avoiding the decompressed bladder (Figure 31.3). This is done to ensure that the distance between the trocar tips and the target organ is not too close; in small children and infants, the distance from the skin to the target may only be 2–3 cm. If a distal ureterectomy is planned after the resected renal moiety is free, then placing the lower port more medial or along the midline infraumbilically is favorable. This affords using the existing port configuration for a manual laparoscopic completion ureterectomy in the pelvis. If the robot is to be used, an additional port may have to be placed below the umbilicus and the robot may need to be undocked and redocked to the lower ports. Because this process is cumbersome and time-intensive, not to mention more invasive since an additional port is required, we prefer laparoscopically dissecting out the distal ureter even if a surgical robot is used for the renal portion of the case.

Once the ports are placed, if a robot is to be used, it is brought in to the patient from the ipsilateral side, with the camera arm being oriented directly on the line drawn from the umbilicus to the center of the kidney, which

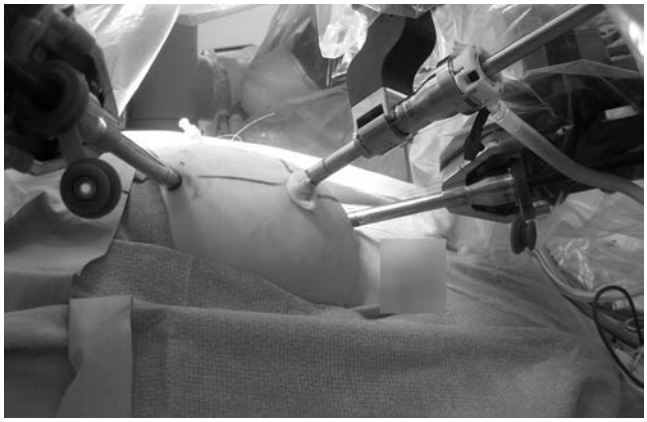

FIGURE 31.3 In-line port positions for left pyeloplasty in the infant. Suprapubic port replaces left anterior iliac crest port position to obtain more distance between this port and the UPJ.

usually is 10°–30° cephalad to the transverse umbilical line (Video 31.1).

NEPHRECTOMY OR HEMINEPHRECTOMY BY TRANSPERITONEAL APPROACH

Once the colon is reflected, identification of the ureter or duplex ureters is performed. In the case of duplex ureters, if the identification or discrimination of the good ureter is in question, we place a stent in the good ureter retrograde at the time of the cystoscopy and retrograde pyelogram. The ureters are followed up to the renal hilum and the unwanted ureter is mobilized. If a heminephrectomy is desired, the ureter is mobilized from underneath the lower-pole renal hilum for an upper-pole heminephrectomy or up to the lower-pole renal pelvis for a lower-pole heminephrectomy. This portion of the surgery is one of the steps that can lead to renal compromise. If too much traction is placed on the healthy vessels while trying to free up the nonfunctioning ureter or pelvis, the healthy pole moiety may experience ischemia temporarily or even permanently.

If an upper-pole partial nephrectomy is planned, identification of the upper-pole vasculature is performed. Many times, these are small vessels that can be treated with cautery; however, if they are greater than 1–2 mm, either titanium clip application or suture ligature can be done. Ensuring that these vessels are indeed the vessels to the unwanted moiety is critical, and identification of the preserved moiety's vessels is helpful in this regard. Once ligation of the vessels is completed, the nonfunctioning moiety may become dusky along the demarcation between the good and divided watershed. This facilitates resection of the moiety. We prefer to use monopolar shears or hook cautery, although using the robotic ultrasonic shears is also a possibility. We do not use the ultrasonic modality because there is no articulation capability. We recommend low cautery settings (<10) when resecting the poor renal cap off of the good moiety, as thermal spread may injure the spared moiety. Once the cap is freed, it can be carefully delivered under the lower-pole vessels. The remainder of the ureter can be mobilized distally to the bladder using either laparoscopy or redocking of the robot. We have used suture ligation as well as Endoloop® ligation or clip ligation for the distal ureterectomy in refluxing systems. Alternatively, if the ectopic system is obstructed, we leave the remaining ureteral end open.

Most moieties are small and can be removed through the umbilical port site. If there is a large cystic component to the moiety, direct laparoscopic needle aspiration can be done to decompress the segment. Occasionally, the umbilical fascial incision will need to be extended underneath the skin to facilitate removal of the specimen.

Inspection of the remaining renal resection bed is necessary to confirm that no violation of the remaining renal moiety's collecting system has been made. If a collecting system tear is recognized, we close with absorbable monofilament suture and try to cover the defect with the lateral and medial edges of the remaining kidney. If a leak is noted, a stent is left in the good ureter. If no stent had been placed prior to the renal surgery, one can be placed by making a small pelvotomy just cephalad to the ureteropelvic junction (UPJ) and passing a stent antegrade. Confirmation of the distal stent position can be made with intraoperative bladder ultrasonography.[18] The ligated hilum is also inspected for bleeding with partial abdominal decompression. All port sites (>2 mm) are closed at the level of the fascia, and any hitch stitches or angiocatheter percutaneous sites are observed for bleeding.

Robotic Considerations

The rules for triangulation are modified in robotics. The ideal transperitoneal robotic port placement follows a gradual arc, with the center usually being the camera port (Video 31.1), for which we use the da Vinci 8.5 mm trocar for the 3D 8.5 mm scope. The reduction in the camera size from 12 to 8.5 mm in 2008 allows for a smaller umbilical incision, which is measureable especially in infants. The 5 mm 2D scope for the robot is no longer available in the newest da Vinci iteration. We have tended to use the 8 mm ports, as opposed to the 5 mm ports, because we feel that the instrumentation is better for the 8 mm setup. The snaked joints of the 5 mm instruments require a longer distance outside of the trocar for the instruments to articulate, and the finest graspers available for the 5 mm ports are not as delicate as the 8 mm Diamond® tip forceps.

Since the robotic ports are not ribbed, they have a tendency to slip out of the thin abdominal wall of infants during rapid desufflation; therefore, we secure the ports to the skin with nylon suture (Video 31.1). This also facilitates drawing back the ports out of the abdominal wall such that only the distal unmarked tip of the trocar is within the abdomen. Care must be taken to observe the movements of the trocars in this position so as not to stress the abdominal wall, since this will bring the "remote center" or the fulcrum of the ports slightly outside of the abdomen in thin patients. If this is observed, the port will need to be pushed in further to prevent trauma to the port site.

Intuitive Surgical recommends maintaining 8–10 cm between the working ports and the camera port, which,

in infants and small children, is unattainable. However, due to the pliability and convexity of the young child's abdominal wall, we find that intertrocar distances as low as 3–4 cm are possible without arm collisions. This is also due to the extremely small field of surgery required. Large distances within the abdomen do not need to be traversed, and initial port placement is the most critical portion that facilitates a successful procedure.

Retroperitoneal Access

Lateral Approach

The patient is placed lateral, with sufficient flexion of the operating table so as to expose the area of trocar placement, between the last rib and the iliac crest. In infants and young children (under 6 years), use lumbar padding to laterally flex the patient without flexing the operating table. Retroperitoneal access is achieved through the first incision, 10 mm in length, and one finger width from the lower border of the tip of the 12th rib (Figure 31.4). The use of narrow retractors with long blades allows a deep dissection despite a short incision. Gerota's fascia is approached by a muscle-splitting blunt dissection; it is then opened under direct vision, and the first blunt trocar (5 or 10 mm) is introduced directly inside the opened Gerota's fascia. A working space is created by gas insufflation dissection, and the first trocar is fixed with a purse-string suture that is applied around the deep fascia to ensure an airtight seal and to allow traction on the main trocar if needed to increase the working space. A second trocar (5 mm) is inserted posteriorly in the costovertebral angle, in front of the lumbosacral muscle. A third trocar (5 mm) is inserted, in the anterior axillary line, a finger width from the top of the iliac crest. To avoid transperitoneal insertion of this trocar, the working space is fully developed and the deep surface of the anterior wall muscles is identified before trocar insertion.

Insufflation pressure does not exceed 12 mmHg, and the CO_2 flow rate is progressively increased from 1 to 3 L/min. Access to the retroperitoneum and creation of the working space are the keys to success in retroperitoneal renal surgery. Age is not a limiting factor for this approach. Young children have less fat, and the access is easier.

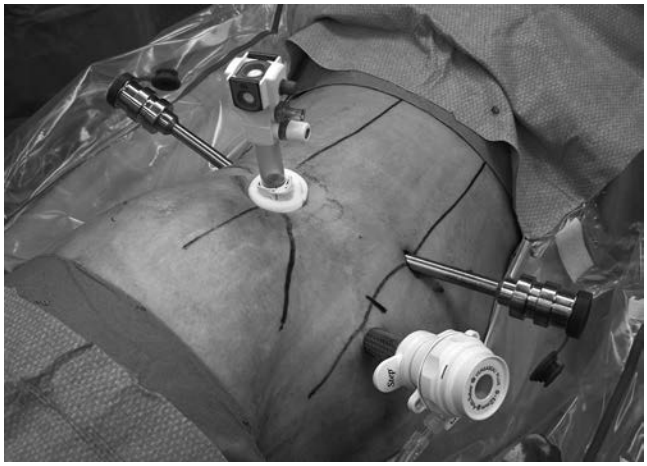

FIGURE 31.4 Port placement for retroperitoneal renal surgery. (Courtesy of Dr. Jim Porter, Swedish Medical Center, Seattle, Washington.)

Prone Posterior Approach

The access begins with an incision in the costovertebral angle at the edge of the paraspinous muscles. The secondary trocars are placed just above the iliac crest, one medially at the edge of the paraspinous muscles, and one laterally at the posterior clavicular line.[19] In a randomized prospective study on 36 complete and 19 partial nephrectomies, Borzi compared the lateral with the posterior retroperitoneal approach in children.[20] There was no significant difference in the operative time.

Other Techniques to Access the Retroperitoneal Space

Since the description by Gaur, balloon dissection has been the method applied by most urologists.[21] Disadvantages of the balloon are the cost of the disposable material and the possible complications related to rupture of the balloon.[22] On the other hand, balloon dissection allows creating a working space without opening Gerota's fascia, which is important for radical removal of malignant tumors in adults. Capolicchio et al. described a modification of lateral access.[23] They recommend the insertion of the first trocar through the costovertebral angle. This modification helped them to avoid an accidental peritoneal tear during access through the first lateral incision, and also allowed a smaller incision for the laparoscope. Micali et al. reported the use of the Visiport visual trocar to access retroperitoneal space directly, which was originally described by Kavoussi.[24] The advantage of this method is the possibility of using a small incision for the first trocar, which is helpful in reconstructive surgery but not in ablative surgery, as the first incision is needed for organ retrieval.

NEPHRECTOMY BY LATERAL RETROPERITONEAL APPROACH

The landmarks of the retroperitoneal space are first identified in order to be oriented with the retroperitoneal exposure. The psoas muscle is the posterior landmark, and should remain in the bottom of the screen. The kidney remains attached anteriorly to the peritoneum, and should remain upward on the screen. The renal pedicle is identified and approached posteriorly; it is dissected close to the junction with the aorta and vena cava, to avoid multiple ligations of branches of the renal vessels. On the left side, the vein is ligated distal to the genital and adrenal branches. On the right side, the vein is short and a careful dissection at its junction with the vena cava will avoid confusion with dissecting the vena cava. After dissecting the renal artery, and then the vein, the vessels are clipped, ligated, or coagulated. In the absence of reflux, the ureter is coagulated and divided at the lumbar level (especially in pretransplant nephrectomy, the native ureter might be used for the transplantation).

In the presence of reflux, the dissection is followed distally, the vas deferens is identified in males, and the ureter is ligated as close as possible to the ureterovesical junction.

During this distal dissection, the surgeon moves toward the head of the child, and the screen goes toward the feet of the child. One can use an Endoloop or a percutaneously passed suture to fix the ureter to the abdominal wall to facilitate its distal dissection and ligation. A fourth trocar is used if the dissection is not sufficiently close to the bladder, and it is inserted at the edge of the lumbosacral muscle close to the iliac crest. As the peritoneum is very close to the ureter in this distal part, its dissection is left at the end of the procedure to avoid an early peritoneal tear. The last part of dissection is the anterior surface of the kidney. The kidney is dissected from the peritoneum very close to its capsule in the cleavage plane of areolar tissue. Usually, no hemostasis is necessary in this plane, whereas in inflammatory adherent kidneys, a sharp dissection with bipolar coagulation may be necessary.

Postoperative Care

We leave a urethral catheter in overnight, and children will typically be discharged the 1 or 2 days after the surgery. No activity, diet, or bathing restrictions are required. Follow-up includes a renal bladder ultrasound to identify any perirenal fluid collections and to assess the residual functional renal pole with Doppler if a heminephrectomy was performed.

Outcomes

Multiple studies have looked at laparoscopic nephrectomy and partial nephrectomy in the pediatric population. Several have compared the outcomes of the laparoscopic technique with the open technique and found it to be safe and efficacious.[25–28] These studies have results suggesting equal success between the laparoscopic and open procedures. The trend of safe and efficacious minimally invasive nephrectomy continues with new research of robotic partial nephrectomy. Lee et al. had good results in nine patients undergoing robotic-assisted laparoscopic partial nephrectomy, again showing that expanded roles of robotic surgery in pediatric urology are not only safe but also efficacious.[16]

Pyeloplasty

The second most common fetal abnormality picked up on antenatal ultrasounds is hydronephrosis, the dilation of the kidney pelvis where urine first collects before draining down the ureters. The incidence of hydronephrosis is 1% of all prenatal ultrasounds; within this group, almost half are due to obstruction at the junction between the kidney pelvis and the ureter. The etiology of the obstruction may be intrinsic or extrinsic. The repair of the obstruction involves dividing the narrowed segment and broadening the cross-sectional area of each end and then suturing the ends back together.[29]

Transperitoneal Approach

We recommend initial bladder decompression with an indwelling urethral catheter to avoid bladder injury upon initial access. A urethral catheter is placed either at the end of the preprocedural cystoscopy and retrograde pyelogram or prior to patient positioning. After draining the bladder, we keep the urethral catheter capped so that the renal pelvis remains distended and prep the catheter into the field so that if fluid needs to be instilled into the bladder for recognition of the ureteral stent, we have immediate and sterile access.

As this is a renal surgery, the patient position is the same as in a nephrectomy described above. Standard robotic renal surgery port placement is carried out with the camera port in the umbilicus. We have frequently observed a natural fascial defect at the umbilicus in many children, facilitating ease of open laparoscopic port placement in a Hasson fashion. For left-sided repairs, we use two working ports. On the right side, we place ports in the same orientation as the left side and occasionally need to add a left lateral subcostal 3–5 mm assist port to retract the. The same robotic considerations stated for nephrectomies above also apply here. The robot will approach the patient from the ipsilateral side cephalad to the umbilical line bisecting the arc created by three ports (Video 31.1).

For most left-sided and some right-sided pyeloplasties, a transmesenteric approach is possible since the renal pelves are frequently very distended and are seen bulging up through the mesenteric veil of the lateral colon. This avoids mobilizing the colon, which can lead to a longer return of bowel function. The patient positioning allows for sweeping the small bowel to the dependent contralateral side, exposing the space between the tented unreflected ipsilateral colon and the residual small bowel. In many children, even adolescents, the mesentery is not laden with fat and remains merely a reflection of the peritoneum, through which a small window (quarter sized) can be made with sharp dissection, avoiding obviously visible mesenteric vessels. Small vessels may be divided, but primary colonic arcade vessels must be preserved.

In many right-sided cases or cases where the mesentery is fatty or the renal anatomy is distorted, the lateral colonic attachments can be taken down to allow the colon to fall medial. Again, we have experienced many right-sided cases where minimal reflection of the colon is required, as the hepatic flexure tends to be thin and broad, usually displaying most of the kidney before any reflection has been done. This in situ approach whereby the kidney is not mobilized and the colon is not disturbed demonstrates an advantage to the robotic approach (Videos 31.2 and 31.3).

Transperitoneal Procedure

A standard Anderson–Hynes dismembered pyeloplasty technique is used.[30] Mobilization of the UPJ is facilitated by first exposing the inferior half of the renal pelvis and the proximal ureter. Judiciously grasping the adventitia and using more indirect retraction techniques minimizes potential tissue trauma. Since only two working ports are used, we utilize percutaneous hitch stitches for stabilization of the renal pelvis and sometimes the ureter (Figure 31.5). These allow for retraction by the bedside assistant and they keep the operative target out of pooled urine that accumulates once the ureter is dismembered. In addition,

FIGURE 31.5 Demonstration of percutaneous hitch stitch through renal pelvis to lift up the operative site.

we have described the use of a 14 G angiocatheter placed percutaneously above the operative site to allow passage of 2 mm off-the-shelf cystoscopic graspers or shears, 4 French open-ended angiocatheters, and antegrade stents for bedside retraction and suture cutting, urine or smoke evacuation, and UPJ stenting with up to 4.8 French JJ stents, respectively.[31] This avoids another laparoscopic port, which could be a potential site for herniation or trauma (Figure 31.6).

If an aberrant crossing lower-pole renal vessel unit is identified compressing the UPJ, the junction must be mobilized from underneath the vessels. In certain circumstances, the lower-pole vessels create extrinsic compression on the UPJ without any intrinsic narrowing. If the ureter is able to be slid cephalad and caudad to the vessels and appears to have a broad luminal cross section, a vasculopexy or vascular hitch procedure may be performed.[32] This requires adequate mobilization of a redundant renal pelvis so that the lower-pole renal vessels may be secured within a renal pelvis wrap. The robot facilitates this maneuver since we use interrupted 3-0 dyed absorbable monofilament stitches to bring the pelvis around the vessels. Special care must be taken to make sure that (1) the final resting position of the vessels is far cephalad to the UPJ and (2) the wrap is not so tight as to constrict blood flow. We check this by placing the tips of a robotic large needle driver between the wrap and the vessels. If the UPJ appears to be intrinsically narrowed, then a standard dismembered pyeloplasty and transposition of the ureter on top of the lower-pole vessels is performed. We have employed the vascular hitch procedure for a few children, although we recommend a conventional dismembered pyeloplasty for most.

Once the UPJ is dismembered, the distal ureter is spatulated along the lateral side and the renal pelvotomy is spatulated along the medial side, facilitating a broad anastomosis at the most dependent portion of the pelvis. This maneuver can be one of the most challenging portions of a pure laparoscopic pyeloplasty but is dramatically facilitated by the articulating robotic instruments. We typically use 5-0 or 6-0 dyed absorbable monofilament suture first, with a few interrupted stitches at the distal apex and then one running stitch along the posterior wall and one along the anterior wall. We have not found the need to reduce the renal pelvis. Prior to anterior wall closure, a 0.025-inch hydrophilic wire loaded with a 3.7 or 4.8 French JJ stent is inserted through the 14 G angiocatheter and driven antegrade down the ureter using the Seldinger technique. Since we pass stents antegrade and not retrograde, we need to confirm placement of the distal stent coil in the bladder, so we employ the use of an off-the-shelf ultrasound (Sonosite, Bothell, Washington), which anesthesia uses for regional blocks to confirm the distal coil.[18] The anterior wall is then closed. We do not close the mesenteric window and have not had a case of internal herniation; however, some describe closing the window merely to provide a safe and easy robotic suturing task for junior trainees. In addition, we do not suture the reflected colon back to the lateral abdominal wall. We do not place abdominal drains other than the JJ ureteral stent. We close all port sites at the level of the fascia under direct vision and make sure that there is no bleeding from the 14 G angiocatheter or hitch stitch puncture sites while the abdomen is partially decompressed. Skin incisions are closed with absorbable monofilament subcuticular sutures and cyanoacrylate skin glue.

FIGURE 31.6 Insertion of percutaneous 14 G angiocatheter (assist port) for venting, antegrade wire and stent passage, and cystoscopic shears and grasper placement.

Robot Considerations

In addition to the robotic considerations in the nephrectomy section, additional tips apply. Since the robot, unlike laparoscopy, does not provide good tactile feedback, surgeons must rely on visual cues to sense potential tissue trauma. This is hardly scientific, and therefore adhering to the principles of delicate open surgery, such as "no touch" processes, is ideal for our pediatric patients. We use a limited number of instruments, such as the Diamond tip forceps, which minimize the trauma to the fine suture material while also providing the least amount of grip strength for potential tissue injury. These are not good for larger children, as they provide very poor tissue-grasping capabilities. We use 8 mm instruments because we use 6-0 monofilament suture material for our anastomosis and have found that the 5 mm needle drivers alter the integrity of the suture; therefore, we use the da Vinci Diamond tip needle drivers for fine suturing. We have not observed large residual port site scars, even in infants, and only one patient to date developed a port site hernia. We close all port sites at the level of the fascia with absorbable braided polyglycolic acid suture. The working ports are placed in the midline below the xiphoid and on the midclavicular line and on the ipsilateral side below the umbilicus (Figure 31.7).

Retroperitoneal Approach

The same access is used as described for nephrectomy. Yeung et al.[33] used different positioning according to the side of the kidney: semiprone for the right side and semilateral for the left side. The three-trocar technique uses one 3 or 5 mm port for the laparoscope at the tip of the 12th rib, a 3 mm port at the costovertebral angle, and a third trocar of 3 mm at the top of the iliac crest. The kidney is approached posteriorly, and the renal pelvis is first identified. The pyeloureteral junction is identified, and a minimal dissection is done to free the junction from connective tissue. Small vessels are divided using bipolar electrocoagulation. Care is taken not to section ureteral blood vessels. A stay stitch is placed at the junction. Aberrant crossing vessels are identified.

The renal pelvis is partially divided using scissors at the most dependent part, and gentle traction on the stay suture helps to define this point. Keeping the traction, the ureter is partially divided and incised vertically for spatulation. The traction suture helps to mobilize the ureter, so the scissors can be in the axis of the ureter, usually introduced through the last trocar. The anterior surface of the kidney is left adherent to the peritoneum, so that the kidney is retracted medially without the need for individual kidney retraction. The ureteropelvic anastomosis begins using a 6-0 absorbable suture, placed from the most dependent portion of the pelvis to the most inferior point or vertex of the ureteral spatulation. The suture is tied using the intracorporeal technique, with the knots placed outside the lumen. The same stitch is used to run the anterior wall of the anastomosis. The UPJ is kept intact for traction and stabilization of the suture line, and removed just before tying the last suture on the pelvis. This stay suture may be fixed to the psoas muscle to give stability and facilitate the suturing. A double-pigtail stent is inserted through the costovertebral angle trocar, and if there is doubt, its position in the bladder is ensured with intraoperative ultrasound, as above. The posterior ureteropelvic anastomosis is then performed. In cases of aberrant crossing vessels, the technique is slightly different. After placement of the stay suture, the ureter is completely divided and the UPJ and the pelvis are delivered anterior to the vessels with the help of the stay suture; then the anastomosis is performed as described.

FIGURE 31.7 Port placement incisions.

Postoperative Care

The majority of our patients are discharged the day after surgery after a successful trial of void and oral intake or analgesia tolerance. We have no activity restrictions, and bathing is permissible immediately. The JJ stents are removed 3–6 weeks after the repair under a brief general anesthetic and cystoscopic procedure. Patients with preoperative hydronephrosis are followed up in 1–2 months with a renal bladder ultrasound, and if there is any equivocation or if the patients initially presented with transient hydronephrosis due to Dietl's crisis, a nuclear renogram is ordered.

Outcomes

Success with both laparoscopic and robotic pyeloplasty is comparable to that with open pyeloplasty.[34] Evidence continues to prove that both modalities have excellent success rates and low complication rates. A recent article by van der Toorn et al. found that laparoscopic pyeloplasty had a 98% success rate and a decreased length of postoperative stay compared with an open pyeloplasty cohort.[35] The case for robotic-assisted pyeloplasty is also mounting, with several recent studies showing not only that it has similar success rates as open pyeloplasty with low complication rates[36,37] but also that practices without prior laparoscopic

experience can transition from open to robotic pyeloplasty with good success.[38]

Other Minimally Invasive Modalities

Laparoendoscopic Single-Site Surgery

In efforts to reduce poor cosmetic outcome and incision sites, laparoendoscopic single-site surgery (LESS) was developed. With this technique, there is a single 10–25 mm incision made transumbilically, through which all of the laparoscopic instruments fit. This is accomplished with either commercially available products or homemade products (one in particular is made with a retractor ring and surgical glove[39]) that allows placement of three or four laparoscopic ports that all enter the body through the umbilical incision. This can result in a "scarless" surgery.

Desai et al. first described the LESS technique for nephrectomy and pyeloplasty in 2008.[40] There have been several papers describing the technique in the pediatric population.[41–44] All had excellent outcomes but remark on the advanced and difficult skill set that is required. This stems from the inherent lack of triangulation of the instruments. The instruments are essentially parallel to each other and in very close proximity. Articulating instruments make this configuration possible. This is a developing area in surgery and certainly an interesting new avenue in pediatric urology.

Endopyelotomy

About the time that laparoscopy was beginning, new endoscopic procedures were also being developed for minimally invasive treatments. The endopyelotomy is a procedure that could be accomplished antegrade or retrograde with a balloon dilator, cold knife, electrocautery, or laser. Several studies have been conducted in children for primary and salvage repair of UPJ obstruction. Unfortunately, success rates have never approached those of open, laparoscopic, or robotic-assisted laparoscopic pyeloplasty. In one study by Patel et al.,[45] adults treated for secondary UPJ obstruction with endopyelotomy had a 83.5% success rate, but children under 5 years of age had a 75% failure rate. Tallai et al.[46] looked at endopyelotomy in 37 children. They had a success rate of 85%, but also two nephrectomies. Endopyelotomy for salvage after failure of pyeloplasty has also not compared well with open, laparoscopic, or robotic-assisted laparoscopic techniques. In one study, Braga et al.[47] compared salvage endopyelotomy to redo open pyeloplasty. The redo open pyeloplasty had a 100% success rate, but the salvage endopyelotomy only succeeded in 39% of patients.

CONCLUSION

The minimally invasive techniques of laparoscopy and robotic-assisted laparoscopic treatment of renal anomalies in the pediatric population are safe and efficacious. Laparoscopy continues to be a reasonable approach, but the steep learning curve and difficult intracorporeal suturing keep it out of reach of many pediatric urologists. Robot-assisted laparoscopic renal surgery is growing in popularity and can be adopted by practices that did not previously perform pure laparoscopic surgery. Many studies have shown that the complication rates and success rates for laparoscopic and robotic-assisted laparoscopic partial nephrectomy, nephrectomy, and pyeloplasty are comparable to those of open procedures. Furthermore, the benefits of decreased hospital stay and postoperative pain after minimally invasive surgery on the kidney have been realized. In the future, these techniques may be able to be performed through single incisions without any resulting scar.

MULTIMEDIA FILES AVAILABLE ONLINE (www.crcpress.com/cw/Docimo)

VIDEO 31.1 Port placement for child renal surgery. Demonstration of port positions access, securing ports, intra-abdominal views, and orientation to target pathology.

VIDEO 31.2 Right robotic pyeloplasty with conventional laparoscopic exposure.

VIDEO 31.3 Left robotic pyeloplasty.

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CHAPTER 32

Wilms' Tumor

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INTRODUCTION

Nephroblastoma, or Wilms' tumor, is an embryonal tumor that develops from the remnants of the immature kidney. It is the most common renal tumor of childhood.

As a result of work performed in the last decades by cooperative groups, survival of children with Wilms' tumor is generally excellent, save for some specific subpopulations. Our advancing capabilities related to molecular staging continue to allow us to identify those who are at higher risk, and require more intense therapy. Simultaneously, those at lower risk are becoming eligible for a reduced therapeutic burden and, we hope, fewer long-term effects. Unfortunately, we are still wanting for new, effective therapeutic agents. Hopefully, the evolving field of cancer pharmacogenomics will address this need. This chapter is a comprehensive review of Wilms' tumor and briefly discusses other less common renal tumors.

EPIDEMIOLOGY

The annual incidence of Wilms' tumor is approximately 7.6 cases per million children under 15 years of age, or about 500 new cases annually in the United States. Wilms' tumor accounts for 6%–7% of all childhood cancers.[1] It typically affects young children (median age 3.5 years), although older children and occasionally even adults can be affected. Wilms' tumor occurs at an earlier age in children with bilateral tumors (median 29.5 months for boys and 32.6 months for girls). The disease occurs nearly equally in girls and boys worldwide.[2]

Children with Wilms' tumor frequently have associated congenital anomalies or recognizable syndromes. Syndromes associated with a predisposition to develop Wilms' tumor may be divided into those characterized by overgrowth and those lacking overgrowth. Syndromes with overgrowth features include hemihypertrophy, which may occur alone or as part of the Beckwith–Wiedemann syndrome (BWS). BWS is a rare disorder, characterized by excess growth at the cellular, organ (macroglossia, nephromegaly, and hepatomegaly), or body segment (limb hemihypertrophy) levels (Figure 32.1).[3] The incidence of tumor development in BWS is 10%–20%. Common cancers in these patients include Wilms' tumor, adrenocortical neoplasms, and hepatoblastoma. The risk of Wilms' tumor development in patients with hemihypertrophy and BWS is estimated to be in the order of 4%–10%, with 21% of those children presenting with bilateral disease.[3–7]

Data from the BWS registry suggest that nephromegaly is a strong risk factor for the subsequent development of Wilms' tumor in this population.[8] The mean age at diagnosis of Wilms' tumor in hemihypertrophy patients is similar to that of the general Wilms' tumor population.[9] Other overgrowth syndromes, such as the Perlman and Simpson–Golabi–Behmel syndromes, are also associated with the development of Wilms' tumor (Table 32.1).[10,11]

Wilms' predisposition syndromes not associated with overgrowth frequently have associated genital or urinary tract anomalies. Genitourinary anomalies (hypospadias, cryptorchidism, and renal fusion anomalies) are present in 4.5% of patients with Wilms' tumor.[12] Denys–Drash syndrome (DDS) represents the specific association of male pseudohermaphroditism, renal mesangial sclerosis, and nephroblastoma. The classic presentation consists of ambiguous genitalia, with up to 40% of children appearing phenotypically female.[13] Genetic studies indicate that DDS is associated with mutations of the 11p13 Wilms' tumor gene.[14] Roughly 1% of Wilms' tumor patients are diagnosed with the WAGR (Wilms' tumor, aniridia, genital anomalies, and mental retardation) syndrome.[15] Most affected individuals have a constitutional deletion on chromosome 11. The incidence of Wilms' tumor formation in these children is 42%. Children with WAGR present at an early age and have lower birth weights and an increased incidence of bilateral disease.[16] Wilms' tumors have also been reported in association with neurofibromatosis, Sotos's syndrome, and Klippel–Trénaunay–Weber syndrome (Table 32.1).[17]

There is an increased risk of Müllerian duct anomalies in girls with Wilms' tumor.[18] Approximately 10% of girls have abnormalities, such as duplication of the cervix or uterus, or bicornuate uterus. Patients with horseshoe kidney have been noted to develop Wilms' tumor at a higher than expected rate.[19,20] Wilms' tumor has been reported in patients with multicystic dysplastic kidney (MCDK), but there is insufficient evidence to support that the incidence is higher than in the general population.[21] The frequency of ultrasound follow-up for children with MCDK and indications for nephrectomy in these patients remain controversial, with some suggesting that no follow-up is needed.[21,22]

FIGURE 32.1 Young female patient with hemihypertrophy.

Surveillance imaging with renal ultrasound has been recommended in children with hemihypertrophy (WAGR), BWS, or aniridia (and other predisposition syndromes), with the intent of discovering tumors at an earlier stage. A review of BWS patients reported by the National Wilms Tumor Study Group (NWTS) found more stage I tumors, and noted that high-risk children undergoing periodic screening have smaller tumor diameters.[7,23] There were not enough patients in this retrospective review to determine if early detection had an impact on patient survival. Craft et al. reported on 13 high-risk children undergoing screening with abdominal ultrasound and did not find any significant difference in stage distribution compared with children not undergoing screening.[24] Nevertheless, screening for high-risk children is recommended, and the suggested interval is every 3–4 months.[25,26] It is important to note that not all new lesions in these children represent a Wilms' tumor, as there is an increased incidence of nonmalignant renal lesions in children with BWS.[27,28]

TABLE 32.1 Syndromes associated with Wilms' tumor and estimated risk of tumor development

Syndrome	Tumor risk
BWS with hemihypertrophy	5%
Perlman	30%–60%
Simpson–Golabi–Behmel	7.5%
Denys–Drash	90%
WAGR	30%–50%
Neurofibromatosis	<1%
Sotos	5%–20%
Frasier	Rare

Unfortunately, nephrectomy has been performed for benign disease due to false-positive screening.

BIOLOGY, GENETICS, AND BASIC RESEARCH

The role of genetic alterations in Wilms' tumor development has been intensely studied. Most Wilms' tumors arise from somatic mutations. These mutations occur in the tumor tissue only, and cannot be transmitted to the progeny of the affected individual. A much smaller percentage of Wilms' tumors (~10%) appear to be the result of germline mutations. Mutations arising in germ cells can be inherited (in some cases, they can also occur de novo). Patients with germ cell mutations are characterized by syndromic conditions, associated congenital anomalies, family history of tumor, and tumors that occur at an earlier age.[29] It was this group of patients that prompted Knudson to suggest that his "two-hit" theory, originally developed by studying children with retinoblastoma, might apply to Wilms' tumor.[30,31] The Knudson model predicts that two genetic events are required for tumor formation. Individuals with a genetic predisposition carry an initial lesion in their germline, either inherited from a parent or resulting from a de novo mutation. In these individuals, all body cells have been affected by the first event. Consequently, only one new event, in any one cell, is required for tumor development. By contrast, in individuals that are not genetically predisposed (sporadic cases), two relatively rare, independent events are required in the same cell. Subsequent genetic studies in a number of tumors have confirmed the Knudson model, demonstrating that the two postulated "genetic hits" constitute the inactivation of both alleles of a tumor suppressor gene.[32] The clearest example of tumorigenesis following the inactivation of both copies of a single tumor suppressor gene is the development of retinoblastoma following the inactivation of the retinoblastoma gene *RB1*.[33] By contrast, the two-hit theory, which was so elegantly confirmed in patients with retinoblastoma, has not stood the test of time in Wilms' tumor. Today it is recognized that the biologic pathways leading to the development of the majority of Wilms' tumors are complex and involve multiple genetic loci.[29,31]

The observation that patients with aniridia, genital anomalies, and mental retardation were at a high risk for Wilms' tumor led to cytogenetic studies that identified a heterozygous deletion at band 11p13 of chromosome 11. Using cloning techniques, the *WT1* gene was identified.[34–36] The chromosome 11p13 locus encompasses various genes, including *PAX6*, in which abnormalities are responsible for aniridia.[37] *WT1* is expressed in the normal-developing kidney and abnormally expressed in some Wilms' tumor specimens. *WT1* encodes a zinc finger transcription factor that is thought to function as a tumor suppressor gene. A partial list of genes that are targets of *WT1* regulation include *EGFR*, *PDGF*, *IGF*, *N-Myc*, *PAX2*, *MDR-1*, and *P-21*, all notable for their association with tumorgenesis.[38] *WT1* mutations have been shown to occur in human DNA from sporadic Wilms' tumor, as well as the germline of patients with a genetic predisposition to cancer.

Although at first *WT1* was considered a classic tumor suppressor gene (i.e., loss of both copies of the gene are required for tumor development), it is now clear that specific alterations in only one of the two *WT1* alleles may contribute to abnormal cell growth and associated genitourinary abnormalities.[32] Normal function of *WT1* is necessary for genitourinary development. Mutations at the *WT1* locus, particularly in males, may confer extensive genitourinary defects, most notably male pseudohermaphroditism.[14,39]

DDS, characterized by pseudohermaphroditism, renal failure, and Wilms' tumor, is the result of point mutations in the binding domain of *WT1*.[14] Interestingly, the kidneys and gonads of patients with DDS are heterozygous for germline mutations. The resulting phenotype is far more severe than that observed in children with a constitutional deletion of one *WT1* allele (i.e., WAGR patients) and suggests that the mutated protein can inhibit the activity of the wild-type protein, resulting in a "dominant negative" effect.[40] A spectrum of phenotypes can be demonstrated by patients with the DDS depending on the type of *WT1* mutation.[29] Interestingly, renal dysfunction, once thought to be limited to those with DDS, is now known to occur years after treatment in patients with WAGR syndrome as well.[16]

In addition to WAGR and Denys–Drash patients, germline mutations have also been found in familial Wilms' tumor. Families harboring a constitutional *WT1* abnormality constitute only a small percentage of the reported pedigrees.[41] Germline *WT1* mutation has been correlated with a predominantly stromal pathology.[42] Constitutional mutations of *WT1* are rarely seen in patients with nonsyndromic, unilateral tumors in the absence of genitourinary abnormalities.[42]

In summary, the majority of Wilms' tumors do not have genetic alterations at chromosome 11p13. Germline *WT1* mutations are associated with genitourinary anomalies. No increased risk of mutation is found in patients with nephrogenic rests (NRs), bilateral Wilms' tumor (BWT), or a family history of Wilms' tumor.[43]

A second potential Wilms' tumor gene, *WT2*, was identified on chromosome 11p15, based on the observation of loss of heterozygosity (LOH) at this site.[44,45] The actual gene responsible remains to be determined, although several candidates genes, such as insulin-like growth factor 2 (*IGF2*), have been proposed.[43] Like the association between *WT1* at chromosome 11p13 and WAGR syndrome, *WT2* has been linked to BWS.[44,46] BWS is an overgrowth disorder that is associated with a 5%–10% risk of Wilms' tumor. Eighty-five percent of BWS cases are sporadic, while 15% are familial.[44] Recent studies suggest that abnormal expression of *IGF2* and the growth repressor *CDKN1C* are involved in the pathophysiology of BWS.[44,47]

A minority of Wilms' tumors are explained by currently described chromosomal abnormalities. For example, *WT1* mutations are only seen in 5%–10% of patients. The search for other candidate genes has continued. In 2007, another putative Wilms' tumor gene was discovered, *WTX*. Located on the X chromosome, the gene was reported to be inactivated in about 33% of Wilms' tumors. Subsequent reports have suggested that the prevalence of *WTX* mutations is less than originally thought, and that these mutations may overlap with *WT1* mutations.[45] Functionally, *WTX* is thought to be a classic tumor suppressor gene impacting both the p53 pathway and β-catenin pathways.[48,49]

Other more recent significant discoveries have included the identification of LOH at chromosome 16q (present in 20% of all Wilms' tumors) or 1p (seen in 10% of tumors) as predictors of poor outcome in children with Wilms' tumor.[50–53] Accordingly, current protocols upstage patients with otherwise favorable histology (FH) if they possess LOH at these sites, hoping that more aggressive treatment will result in better outcomes for this subgroup.

Recently, utilizing comparative expressed sequence hybridization (CESH), investigators have discovered that abnormalities in expression of the long arm of chromosome 1q were associated with relapse and worse outcome in a subset of patients with FH Wilms'.[54] A study from the Italian cooperative looked at 77 patients and found that copy number gains at chromosome region 1q21.1–q31.3 were significantly associated with relapse, confirming earlier findings. Therefore, chromosome 1q abnormalities have become a target of interest for staging and risk stratification by the Children's Oncology Group's (COG) Renal Tumor Committee.

Alterations of the *p53* tumor suppressor gene located on chromosome 17p have been noted in approximately 75% of anaplastic tumors, suggesting an important role in the development of anaplasia.[55,56] By acting as a downregulator of cell proliferation and a positive regulator of cellular apoptosis, *p53* is known to play a significant role in tumor suppression. Malkin et al. suggested that the absence of *p53* is an indicator of advanced disease in Wilms' tumor, regardless of the presence of anaplastic changes.[57] Comparative genomic hybridization studies and immunohistochemical analysis have confirmed an association between chromosome 17p (*p53*) abnormalities and tumor aggressiveness.[58,59]

HISTOPATHOLOGY

Wilms' tumor is an embryonal tumor that grows to compress the adjacent normal renal parenchyma, forming a pseudocapsule composed of condensed, atrophic renal tissue. This intrarenal pseudocapsule is an important distinguishing feature. Most tumors are soft and friable, with necrotic or hemorrhagic areas frequently noted. This consistency increases the chance of intraoperative tumor rupture, which can predispose to local tumor recurrence.

Wilms' tumor is characterized by histologic diversity. Classically, a triphasic pattern is seen that includes varying proportions of three cell types: blastemal, stromal, and epithelial (Figure 32.2). Some tumors may only consist of biphasic or even monomorphous patterns. These varied components respond differently to treatment, which can impact outcome.[60] In addition to demonstrating cell types found in a normal-developing kidney, Wilms' tumor often contains tissues such as skeletal muscle, cartilage, and squamous epithelium. These heterotopic cell types probably reflect the primitive developmental potential of the metanephric blastema not seen in

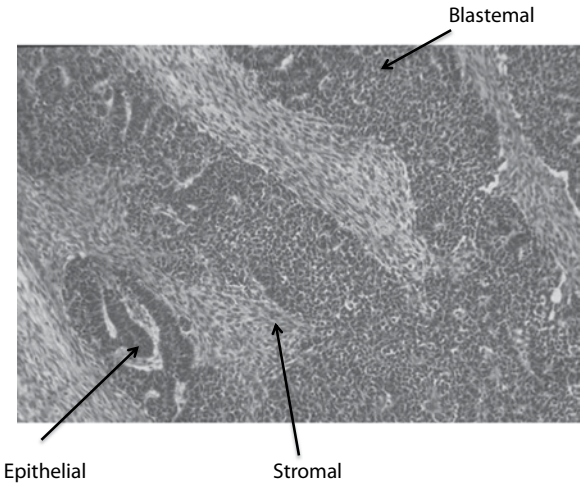

FIGURE 32.2 Triphasic Wilms' tumor.

normal nephrogenesis. Most Wilms' tumors are typically unicentric, but up to 12% may be multicentric unilateral tumors.[9] Extrarenal locations are rare and are thought to arise from displaced metanephric elements or mesonephric remnants.[61,62]

Wilms' tumor is classified as having FH when epithelial, blastemal, or stromal elements are found in the absence of anaplasia.[63] Tumors with large nuclei, abnormal mitotic figures, and hyperchromasia are anaplastic, or *unfavorable*, and are associated with increased rates of relapse and death (Figure 32.3).[63] These unfavorable features were found in approximately 10% of patients, but accounted for almost half of the tumor deaths in early NWTS studies.[64] Anaplasia is rare in the first 2 years of life, but the incidence increases with age at presentation.[65] It is primarily associated with resistance to chemotherapy. A similar incidence of anaplasia has been observed in NWTS studies and in the International Society of Pediatric Oncology (SIOP) study (5.3%).[66] Anaplasia is further classified as focal or diffuse. Focal anaplasia requires that cells with anaplastic nuclear changes be confined to sharply restricted foci within the primary tumor.[67] Diffuse anaplasia is diagnosed when anaplasia is present in more than one portion of the tumor or is found in any extrarenal or metastatic site; it is a harbinger of poor prognosis. When the anaplastic component is completely removed, the outcome is generally excellent.[68] This supports the contention that anaplasia is an indicator of chemoresistance, not inherent aggressiveness of the tumor.

Clear cell sarcoma of the kidney (CCSK) and rhabdoid tumor of the kidney (RTK) were previously grouped as unfavorable histology Wilms' tumors. They are now recognized as separate malignant entities.[69–71]

NRs represent the abnormal persistence into postnatal life of embryonal cells that can involute, sclerose, disappear, or produce a malignancy (Figure 32.4).[72] NRs are seen in 35% of patients with a unilateral Wilms' tumor and nearly 100% with bilateral Wilms'. NRs have been detected in up to 1% of kidneys in infants on postmortem examination; most of these rests undergo involution.[73] It is estimated that less than 1% of NRs will eventually become Wilms' tumor.[74] Two distinct categories of NRs exist, based on the position of these lesions within the kidney. Perilobar nephrogenic rests (PLNRs) are confined to the periphery of the renal lobe, likely developing late. They are seen in 1% of infant autopsies. Intralobar nephrogenic rests (ILNRs) occur within the renal lobe or other sites, including the renal sinus and collecting system. They are associated with an early renal developmental event and are seen less frequently on infant postmortem exam (0.1%). There are biologic differences distinguishing PLNR from ILNR (Table 32.2). ILNR can become cystic and be indistinguishable from renal dysplasia; they are more commonly associated with *WT1* mutations, DDS, and WAGR syndrome. PLNRs are associated with BWS and hemihypertrophy and demonstrate 11p15 abnormalities.

Hyperplastic NRs can produce a renal mass easily mistaken for a small Wilms' tumor.[73] Biopsy of a hyperplastic rest is of little value in distinguishing this lesion from a Wilms' tumor unless the interface between the rest and the normal kidney is sampled.

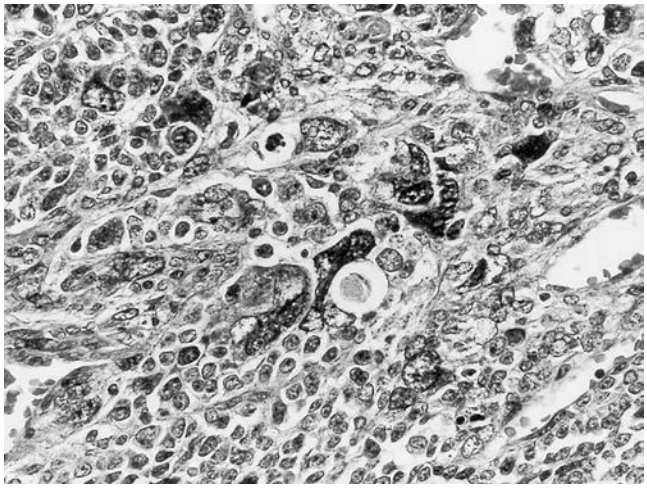

FIGURE 32.3 Anaplastic Wilms' demonstrating large irregulary shaped nuclei.

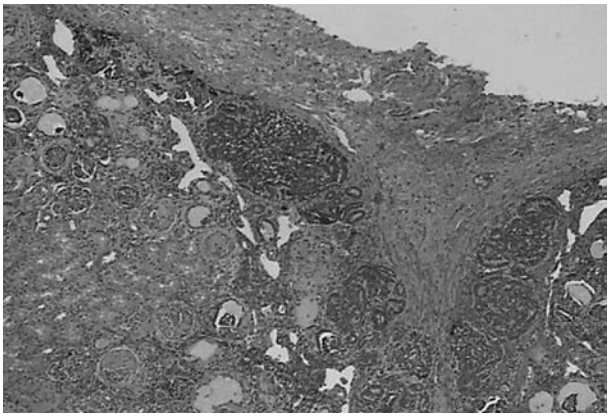

FIGURE 32.4 Perilobar nephrogenic rest composed of blastemal cells just beneath the renal capsule (hematoxylin and eosin, ×40).

TABLE 32.2 Nephrogenic rests and their known associations

	ILNR	*PLNR*
Associated syndromes	WAGR Denys–Drash	BWS, hemihypertrophy Perlman
Median age of Wilms' Tumor development (months)	23	36
Wilms' tumor histology	Stroma/ blastema predominant	Blastemal/epithelial predominant

Wilms' tumor will have a pseudocapsule at the interface, with the normal parenchyma compressing the normal elements; this will be absent in hyperplastic rests.

On imaging, Wilms' tumor will have a spherical shape, whereas hyperplastic rests will be more elliptical or lenticular in shape. Magnetic resonance imaging (MRI) may be of some value in distinguishing between the two lesions.[75]

The presence of multiple or diffuse NRs will lead to the diagnosis of nephroblastomatosis.[76] Nephroblastomatosis can be subclassified according to the rest categories present. Diffuse hyperplastic perilobar nephrogenic rest (DHPLNR) is a particular category in which the majority of the cortical surface of one or both kidneys is composed of hyperplastic NRs. The entire nephrogenic zone is involved, with a thick rind capping the entire kidney (Figure 32.5). These patients are prone to Wilms' tumor development, and bilateral lesions are common. Perlman et al. have reviewed 52 cases of DHPLNRs reported to the NWTS pathology center.[77] Wilms' tumor developed in 23 patients at a median age of 30 months. Of children receiving adjuvant therapy at diagnosis, 52% (17/33) developed a Wilms' tumor. Multiple rests in one kidney usually implies that NRs are present in the other kidney.[73] Children younger than 12 months diagnosed with Wilms' tumor who have NRs have a markedly increased risk of developing contralateral disease.[78] They need regular imaging surveillance to detect contralateral recurrence.[79] The occurrence of metachronous Wilms' tumor in patients previously treated with conventional chemotherapeutic regimens suggests that NRs are not always eradicated.

PRESENTATION, PREOPERATIVE EVALUATION, AND STAGING

Most children with Wilms' tumor present with an asymptomatic abdominal mass. Other signs and symptoms at diagnosis are abdominal pain, gross hematuria, and fever. Occasionally, a child will present with an acute abdomen due to tumor rupture and associated hemorrhage into the peritoneal cavity. Other atypical presentations may result from compression or invasion of adjacent structures (e.g., extension of the tumor into the renal vein and inferior vena cava [IVC]). Varicocele due to gonadal vein obstruction, hepatomegaly due to hepatic vein obstruction, ascites, and congestive heart failure are found in fewer than 10% of patients with intracaval or atrial tumor extension.[80]

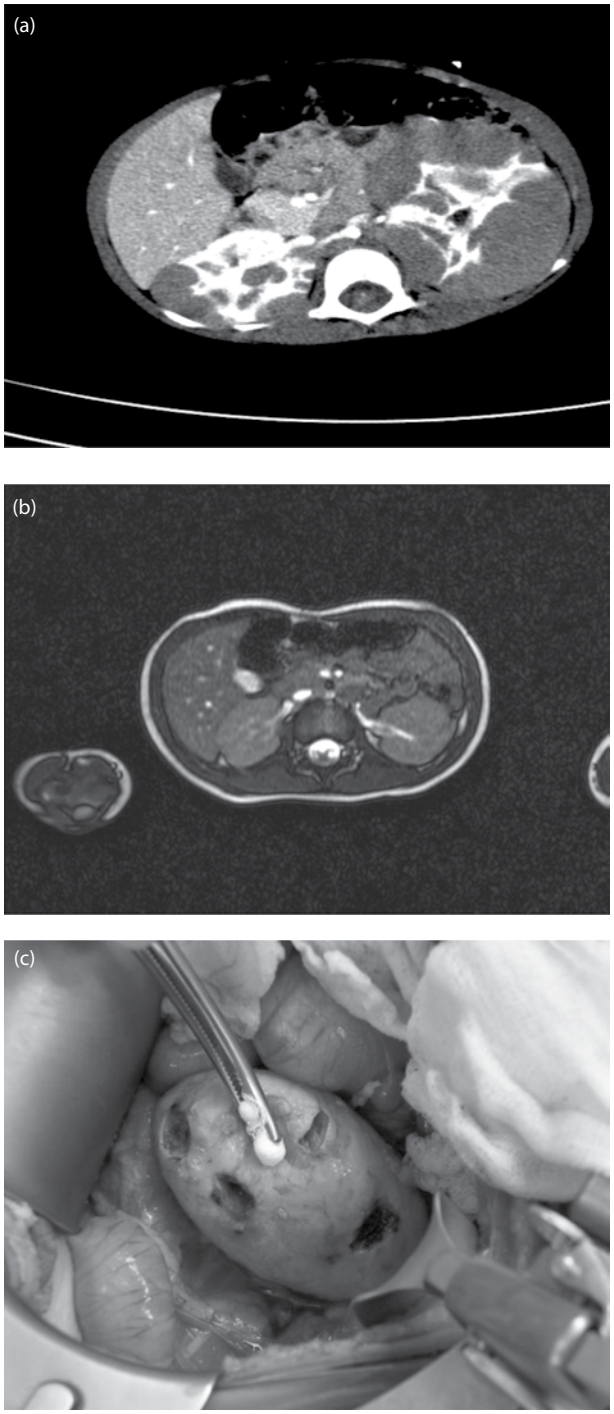

FIGURE 32.5 (a) Pretreatment MRI of bilateral DHPLNR. (b) Postchemotherapy MRI of same patient. (c) Same patient at time of intraoperative biopsy. Note the characteristic "rind" on the surface of the kidney.

Hypertension is present in 25% of cases and has been attributed to elevated plasma renin levels.[81] During the physical examination, it is important to note any physical findings of associated Wilms' tumor syndromes, such as aniridia, hemihypertrophy, and genitourinary anomalies. The preoperative evaluation can generally be completed in 48 hours. Emergent operation is never necessary unless there is evidence of active bleeding or tumor rupture (even

in these rare circumstances, stabilization, volume resuscitation, and blood product replacement should be the first consideration). Laboratory evaluation should include a complete peripheral blood count, platelet count, renal function tests, liver function tests, serum calcium, and urinalysis. Elevation of the serum calcium can occur in children with congenital mesoblastic nephroma (CMN) and RTK. Acquired von Willebrand's disease has been found in 8% of newly diagnosed Wilms' tumor patients.[82]

The preoperative imaging evaluation of children with a solid abdominal mass has evolved over the years. The first study obtained is a renal ultrasound, which can determine if the mass is predominantly solid or cystic. In high-risk children with congenital anomalies or familial syndromes, sonogram may be repeated every 3–4 months for screening. Contrast-enhanced computed tomography (CT) or MRI of the abdomen is obtained next. All the solid renal tumors of childhood have similar radiographic features. However, defining the exact histology is not as important as establishing that there is a solid renal tumor present, which will help the surgeon plan for an operation. Another important role of imaging studies is to establish the presence of a functioning contralateral kidney prior to nephrectomy.[83] More recently, as more nephron-sparing techniques are being adopted, clearly defining local anatomic relationships has become critical for preoperative planning. The radiologist should exclude intracaval tumor extension, which occurs in 4% of Wilms' tumor patients (Figure 32.6).[80] This can usually be excluded on ultrasound, but MRI is the study of choice if extension of tumor into the IVC cannot be excluded by ultrasound.[84]

There is some controversy regarding the utility of preoperative imaging for tumor staging.[79,85,86] Accurate staging of children with Wilms' tumors is essential to define tumor extent prior to initiating treatment, as outcome is highly correlated with stage.[87] However, the staging system used in prior NWTS studies and current COG studies relies on surgical findings and pathologic examination (Table 32.3). Local tumor burden (e.g., regional lymph node involvement) determines the intensity of the chemotherapy regimen and whether a child receives abdominal irradiation. Preoperative CT can certainly identify regional adenopathy, but enlarged benign retroperitoneal lymph nodes are common in children. Correlation between pathologic findings and lymph node evaluation at surgical exploration in Wilms' tumor patients has found high false-positive and false-negative error rates.[88] Detection of extrarenal tumor extension into the perirenal fat and into adjacent structures is also problematic. Most children identified as having possible invasion of the liver on CT are found at the time of surgical exploration to have hepatic compression, rather than hepatic invasion.[89] Therefore, determination of inoperability must be made at surgical exploration. Nonopacification of the kidney on CT may result from tumor obstruction of the collecting system, complete replacement of the renal parenchyma with neoplasm, or intravascular tumor extension.[80,90]

Traditionally, plain chest radiographs were obtained to determine whether pulmonary metastases were present. However, over time most North American institutions began obtaining CT of the chest in the initial evaluation of children with Wilms' tumor. This can detect small lesions missed on chest x-ray (CXR), although the management of such lesions is debated.[91,92] A recent report from COG evaluated event-free survival (EFS) and overall survival (OS) for patients with CT-only pulmonary lesions.[93] Patients with FH and isolated lung lesions found on CXR or chest

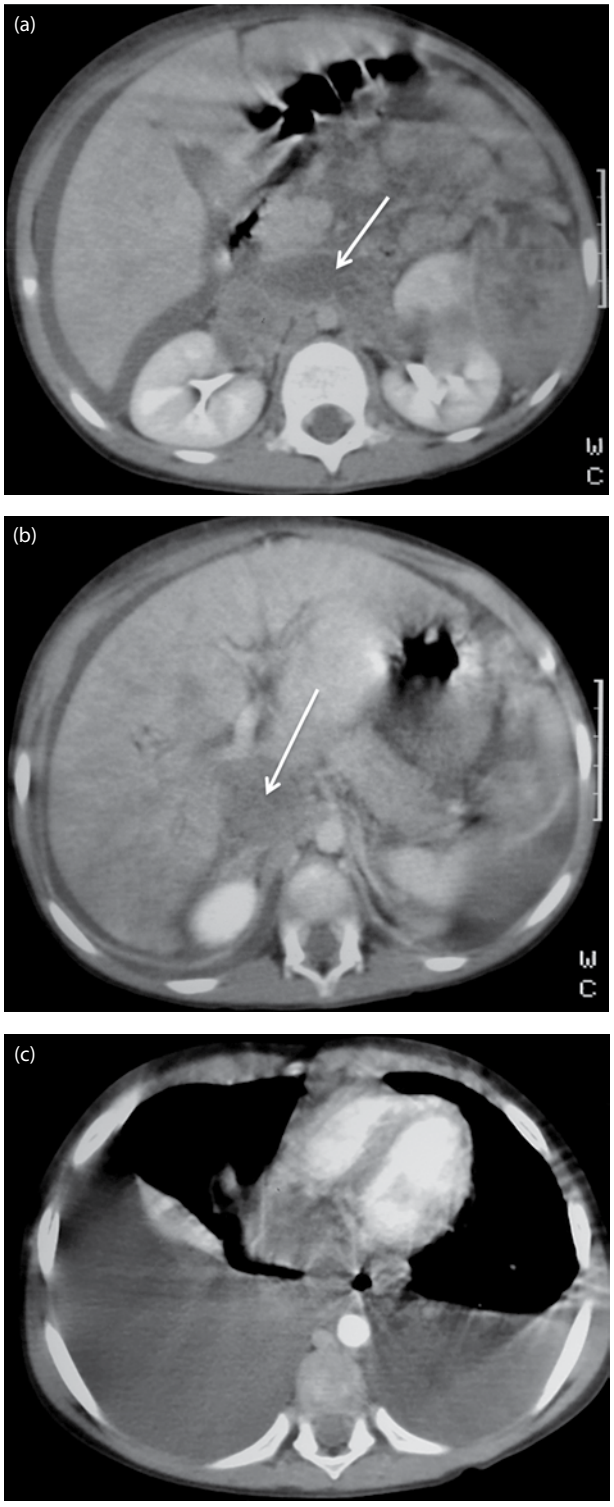

FIGURE 32.6 Renal vein and IVC involvement in a 5-year-old male who presented with shortness of breath and bilateral leg swelling. (a) Left-sided tumor with left renal vein thrombus (arrow). (b) IVC thrombus (arrow). (c) Atrial thrombus.

TABLE 32.3 COG staging system for Wilms' tumor

Stage	Findings
I	The tumor is limited to the kidney and was completely excised. The renal capsule has an intact outer surface. The tumor was not ruptured or biopsied prior to removal (fine-needle aspiration biopsies are excluded from this restriction). The vessels of the renal sinus are not involved. There is no evidence of tumor at or beyond the margins of resection.
II	The tumor extends beyond the kidney, but was completely excised. There may be regional extension of tumor (i.e., penetration of the renal capsule or extensive invasion of the renal sinus). The blood vessels outside the renal parenchyma, including those of the renal sinus, may contain tumor. The tumor was biopsied (except for fine-needle aspiration), or there was spillage of tumor before or during surgery that is confined to the flank, and does not involve the peritoneal surface. There must be no evidence of tumor at or beyond the margins of resection.
III	Residual nonhematogenous tumor is present, and confined to the abdomen. Any one of the following may occur: (1) Lymph nodes within the abdomen or pelvis are found to be involved by tumor (renal hilar, para-aortic, or beyond). (Lymph node involvement in the thorax or other extra-abdominal sites would be a criterion for stage IV.) (2) The tumor has penetrated through the peritoneal surface. (3) Tumor implants are found on the peritoneal surface. (4) Gross or microscopic tumor remains postoperatively (e.g., tumor cells are found at the margin of surgical resection on microscopic examination). (5) The tumor is not completely resectable because of local infiltration into vital structures. (6) Tumor spill not confined to the flank occurred either before or during surgery.
IV	Hematogenous metastases (lung, liver, bone, brain, etc.), or lymph node metastases outside the abdominopelvic region are present.
V	Bilateral renal involvement is present at diagnosis. An attempt should be made to stage each side according to the above criteria on the basis of the extent of disease prior to biopsy or treatment.

CT in NWTS-4 and NWTS-5 were compared with those with CT-only pulmonary findings. Patients with CT-only pulmonary lesions experienced improved EFS if given doxorubicin (DOX) in addition to dactinomycin (AMD) and vincristine (VCR), regardless of whether pulmonary radiation was given. In Europe, where preoperative chest CT is not routine, investigators of SIOP 2001 sought to determine if patients with CT-only pulmonary nodules experience worse outcomes than those patients with localized disease.[94] They found that EFS and OS was worse if pulmonary nodules were seen on CT than if patients had localized disease, but superior to patients who had metastatic disease. Additional imaging studies are helpful under specific conditions. For example, a radionuclide bone scan and x-ray skeletal survey should be obtained postoperatively on all children with CCSK.[95] Brain imaging, using MRI or CT, should be performed.

There is an emerging role for positron emission tomography/computed tomography (PET-CT) in the diagnosis, evaluation, and monitoring of Wilms' tumor.[96,97] A multi-institutional study of 27 patients who had PET-CT performed for suspected disease relapse and progression, and for monitoring of therapy, found that PET-CT was useful for evaluating Wilms' tumor given its metabolic activity.[96] However, pulmonary nodules of <1 cm were not well visualized in this study. A smaller study specifically evaluating the role of fluorodeoxyglucose ($F^{18}FDG$) PET-CT after preoperative chemotherapy found that active Wilms' tumor was still avid, and that higher uptake values were observed in histologically high-risk disease.[97]

The NWTS had previously recommended formal exploration of the contralateral kidney in all children undergoing nephrectomy for presumed unilateral Wilms' tumor. This has been considered necessary to identify lesions that might be missed on preoperative imaging. If lesions are identified intraoperatively, biopsy alone of the lesions is advised and definitive surgical resection is deferred for both kidneys. Review of NWTS-4 patients with BWT found that 7% of lesions were missed on preoperative imaging studies.[98] Most lesions were managed with biopsy alone, yet extended follow-up of the children has not demonstrated any relapses.[99] The majority of these children had nephrectomy of the more involved kidney at diagnosis before exploration of the contralateral kidney. This was also noted in a recent report of NWTS-5 patients.[100] The conclusion of the latest report was that routine exploration is not necessary, provided that preoperative imaging with thin slices on multidetector helical CT scanners or MRI is performed.[99]

SURGERY

The surgeon has an important role in the management of a child with Wilms' tumor. Tumor necrosis, friability, and hemorrhage make these usually large lesions more prone to rupture, increasing morbidity or causing upstaging. Careful removal of the tumor without rupture or spill is essential to decrease the risk of local abdominal relapse.[101] In a retrospective review of 515 patients with favorable histology in NWTS-3 and NWTS-4 who had tumor spillage, 7.3% were found to have recurrent disease.[102] Those who were treated with 10–20 Gy of radiation had lower recurrence rates. Barber et al. evaluated potential preoperative risk factors for intraoperative tumor spillage in a retrospective review of 67 patients from 2000 to 2008.[103] They examined patient age, sex, body weight, tumor capsular thickness, and stage and found the only significant correlation was preoperative tumor volume of >1000 cc. Complete tumor resection also improved patient survival.

Another critical surgical objective is determining tumor stage. A transperitoneal approach is preferred to exclude tumor extension, metastases, or peritoneal seeding. Exploration of the contralateral kidney is no longer mandated prior to nephrectomy if the preoperative CT or MRI demonstrates a normal kidney. If exploration is needed, the colon is reflected and Gerota's fascia opened so that the kidney can be inspected on all surfaces. Any abnormalities of the kidney should be biopsied to exclude Wilms' tumor or NRs. Palpation of the renal vein and IVC should be performed to exclude intravascular tumor

extension prior to vessel ligation. A radical nephrectomy with partial ureterectomy is performed. While a formal lymph node dissection is not required, lymph node sampling is an integral step during surgery for Wilms' tumor.[88] Lymph node metastases (stage III) have an adverse outcome on survival. A recent study looking at patients with stage III disease found that those with lymph node–positive disease faired worse than those who did not have lymph node involvement with 4-year disease-free survival of 73% versus 98%, respectively.[104] The negative impact of LN involvement was further delineated in a study from NWTG-4 and NWTG-5, which showed that positive nodes had worse 5-year EFS, especially in the setting of anaplastic histology.[105] This study also found that the percentage of positive nodes increased as the size of the surgical nodal packet increased. Failure to sample lymph nodes has been identified as a risk factor for local relapse in stage I patients, suggesting that inadequate staging can have significant consequences.[106]

In patients with metastatic disease (most commonly pulmonary metastases), there may be a role for metastasectomy, especially if there is a good response to chemotherapy. In patients who do not respond or experience disease progression, surgical resection metastectomy is unlikely to be helpful.[107,108]

Surgery is not without morbidity and may result in both acute and late complications. A review of NWTS-4 patients undergoing primary nephrectomy found an 11% incidence of surgical complications.[83] The most common complications were hemorrhage and small bowel obstruction. Risk factors associated with increased surgical complications are higher local tumor stage, intravascular extension, en bloc resection of other visceral organs, and incorrect preoperative diagnosis.[83]

TREATMENT AND OUTCOME

The development of effective systemic chemotherapy in the 1960s rapidly changed the outcome and approach to treatment of Wilms' tumor.[109] Randomized trials have been conducted by NWTS, now the COG, as well as SIOP, and the United Kingdom Children's Cancer Study Group (UKCCSG) to determine the appropriate role of available therapeutic modalities in an effort to improve clinical outcomes while minimizing potential side effects and late sequelae. Patients are stratified into different treatment groups based on histopathology and the extent of disease. Despite markedly different initial treatment approaches, outcomes between the major international study groups are quite similar.

National Wilms Tumor Study Group and Children's Oncology Group

The NWTS merged with three other groups in 2000 to form the COG.[110] Initial management of Wilms' tumor has always consisted of up-front nephrectomy, with subsequent management strategy based on histology, surgical staging, and radiologic results. The first three NWTS studies, NWTS-1 (1969–1973), NWTS-2 (1974–1978), and NWTS-3 (1979–1986), showed that postoperative local irradiation was unnecessary for stage I and II FH patients when VCR and AMD were used in combination.[111,112] The addition of DOX to VCR and AMD, in conjunction with radiotherapy, improved EFS for patients with stage III/IV disease. In this series of studies, the staging system was refined as knowledge about histology and other prognostic factors, such as lymph node status, was gained.[87,111–113] The intensity of therapy for the majority of low-risk patients was able to be successfully decreased. This was especially beneficial in limiting the use of the cardiotoxic drug DOX, while still successfully treating patients. There was no statistically significant improvement in survival when cyclophosphamide was added to the three-drug regimen in NWTS-3.

The NWTS-4 (1986–1994) utilized "pulse-intensive" chemotherapy regimens, employing single doses of AMD and DOX, in attempts to limit both treatment toxicity and cost. Pulse-intensive regimens utilized simultaneous administration of agents at less frequent intervals and limited duration to decrease the number of clinic visits, and hence the cost of cancer treatment. NWTS-4 demonstrated that while the administered drug dose–intensity was greater on pulse-intensive regimens, these regimens produce less hematologic toxicity than the standard regimens.[114] Patients treated with pulse-intensive regimens achieved equivalent survival compared with those treated with standard chemotherapy regimens.[100] Treatment with 6 months of chemotherapy was noted to be as effective as treatment with 15 months.

Children with anaplastic Wilms' tumors were randomized in NWTS-3 and NWTS-4 to receive VCR, AMD, and DOX, or those three drugs with the addition of cyclophosphamide. The results were analyzed after the tumors were reclassified using the criteria of Faria et al.[67] There was no difference in outcome between the regimens for children with focal anaplasia, who had a prognosis similar to that for FH patients.[115] For stage II–IV diffuse anaplasia, the addition of cyclophosphamide to the three-drug regimen improved the 4-year relapse-free survival (RFS) rate (27.2% vs. 54.8%).

NWTS-5 (1995–2002) was a single-arm therapeutic trial without any randomization for therapy. Prospective collection of information regarding biologic features of the tumors was part of this study. As a result, collection of banked tumor specimens is available to evaluate new prognostic factors that may be identified in the future. Most importantly, clinical outcome is available for these patient-banked specimens. Based on the results of patients with anaplastic disease in NWTS-3 and NWTS-4, NWTS-5 incorporated cyclophosphamide into the treatment plan for patients with stage II–IV diffuse anaplastic Wilms' tumor.

A central goal of the study was to verify the preliminary finding that LOH for chromosomes 16q and 1p identified patients at increased risk for relapse and death.[51] Among patients with stage I and II FH tumors, the relative risk (RR) of relapse and death was increased for LOH 1p only (RR = 2.2 for relapse; RR = 4.0 for death), for LOH 16q only (RR = 1.9 and RR = 1.4), and for LOH for both regions (RR = 2.9 and RR 4.3) in comparison with patients lacking LOH at either locus.[52] The risks of relapse and death for patients with stage III and IV FH

tumors were increased only when LOH occurred in both regions (RR = 2.4 and RR = 2.7). As a result, LOH for these chromosomal regions can now be used as an independent prognostic factor, together with disease stage, to target intensity of treatment.

A unique aspect of the NWTS-5 trial was that a select group of patients of <2 years of age with stage I FH tumors, weighing <550 g, were managed with surgery alone. This was based on a prior observation of favorable outcomes in a small number of such patients in which postoperative adjuvant therapy had been omitted.[116] A long-term analysis of this cohort revealed a much greater than anticipated salvage rate for the chemotherapy-naive patients who relapsed. Overall, survival between those treated with surgery or chemotherapy were not statistically different despite a higher rate of relapse in those treated with surgery alone (84%) versus those treated with chemotherapy (97%).[117] The current COG protocol, AREN0532, will observe this very low-risk group after surgery alone. Further analysis of this population investigating the effects of body weight and body mass index (BMI) on EFS found no relationship with these factors even when stratified by risk group or age.[118]

All protocols today occur under the auspices of the COG Renal Tumor Committee trials. The current full clinical trials are available through an individual institution's principal investigator. (Table 32.4 shows the current protocol, and Table 32.5 shows the most recently completed studies with survival.) Some highlights from these studies, which include AREN0533, AREN0321, and AREN0534, follow. AREN0533 will investigate patients with stage III or IV FH Wilms' tumor with pulmonary metastases. Patients with pulmonary nodules will be treated with VCR, AMD, and DOX for 6 weeks in the hopes of limiting or eliminating the need for pulmonary irradiation. Chest CT that reveals disappearance of nodules will result in continuation on the three-drug regimen, while incomplete response will be treated with radiation therapy (XRT) in conjunction with AMD, DOX, cyclophosphamide, and etoposide.

Patients with anaplastic Wilms' tumor are being evaluated under COG protocol AREN0321, which hopes to improve clinical outcomes in this high-risk group. Alternating regimens of VCR, etoposide, carboplatin with VCR, DOX, and cyclophosphamide are being given.

Finally, COG has recently opened study protocol AREN0534, which allows for nephron-sparing surgery (NSS) in children with tumor predisposition syndromes and unilateral Wilms' tumor, given the increased risk for renal failure or future bilateral disease.[119,120] The goal is to maximize future renal function by sparing the noncancerous renal parenchyma. On current protocols of COG, the importance of lymph node sampling is stressed, and *all* children with tumor rupture are treated as stage III with more intensive therapy.[110]

TABLE 32.4 Summary of current COG treatment protocol recommendations

Renal tumor	Protocol
FH Wilms' (very low risk/standard risk)	AREN0532
FH Wilms' (standard/higher risk)	AREN0533
Bilateral	AREN0534
Anaplastic Wilms' Clear cell sarcoma Malignant rhabdoid Renal cell carcinoma	AREN0321
Other (low risk)	Follow-on AREN03B2

International Society of Pediatric Oncology

The clinical protocols conducted by SIOP differ from the North American protocols in that therapy is given before surgery, with the goal of reducing the risk of intraoperative rupture or spill by pretreating with chemotherapy.[121] It is also postulated that the neoadjuvant therapy will treat micrometastases, leading to a more favorable stage distribution at the time of surgery.

The first two SIOP studies answered questions with regard to the use of prenephrectomy XRT.[121] The third SIOP study showed that 4 weeks of AMD and VCR was as effective as prenephrectomy XRT in avoiding surgical tumor rupture and increasing the proportion of patients with low-stage disease.[122] SIOP-6, the fourth SIOP study on Wilms' tumor, demonstrated that patients with postnephrectomy stage I disease can safely be treated with 18 weeks of AMD and VCR.[123] Those patients with stage II lymph node–negative disease, however, were shown to have a higher rate of relapse if postoperative abdominal irradiation was omitted. It was concluded that these children require more intensive postnephrectomy chemotherapy, including the use of an anthracycline.[123] Finally, SIOP-6 confirmed the need for a three-drug chemotherapy regimen following nephrectomy for those with more advanced stage disease (i.e., stage II lymph node positive and stage III). The fifth SIOP Wilms' tumor trial, SIOP-9 (1987–1991), evaluated the duration of prenephrectomy chemotherapy. The number of postchemotherapy stage I patients was similar after either 4 or 8 weeks of therapy (64% vs. 62%), and the 2-year EFS was equivalent.[124] Also, there was no significant additional tumor shrinkage benefit after 4 weeks of preoperative chemotherapy.[124] Children with stage II N0 disease were treated with VCR, AMD, and an anthracycline for 27 weeks without XRT, whereas children with stage II N1 and III disease were given the same regimen and abdominal irradiation. The 2-year EFS and OS for stage II N0 was 84% and 88%, and for stages IINI and III it was 71% and 85%, respectively. There were 59 children with stage I–IV tumors who had complete tumor necrosis induced by chemotherapy, and 98% of these children had no evidence of disease at 5 years.[125]

SIOP 93–01 (1993–1999) evaluated a reduction in postoperative therapy for patients with stage I intermediate-risk anaplastic Wilms' tumor.[126] Patients were randomized to receive either 4 or 18 weeks of postoperative chemotherapy with AMD and VCR. Two-year EFS was 91.4% after 4 weeks and 88.8% after 18 weeks of therapy, demonstrating that survival can be maintained while shortening the duration of postnephrectomy therapy. Further retrospective analysis of this study population found that initial tumor volume does impact the risk of finding positive nodes at the time of surgery, while the

TABLE 32.5 Recent completed Wilms' tumor treatment trials and survival

Stage	Histology	Treatment	4-year survival
I	FH of <24 months, tumor weight of <550 g	Surgery only (as part of a clinical trial)	98% OS, 85% RFS
	FH of >24 months, tumor weight of >550 g	Nephrectomy + lymph node sampling followed by regimen EE-4A	98% OS, 94% RFS
	DA	Nephrectomy + lymph node sampling followed by regimen EE-4A and XRT	79% OS, 68% EFS
II	FH	Nephrectomy + lymph node sampling followed by regimen EE-4A	98% OS, 86% RFS
	FA	Nephrectomy + lymph node sampling followed by abdominal XRT and regimen DD-4A	80% OS, 80% EFS
	DA	Nephrectomy + lymph node sampling followed by abdominal XRT and regimen I	82% OS, 83% EFS
III	FH	Nephrectomy + lymph node sampling followed by abdominal XRT and regimen DD-4A	94% OS, 87% RFS
	FA	Nephrectomy + lymph node sampling followed by abdominal XRT and regimen DD-4A	100% OS, 88% RFS
	FA (preoperative)	Preoperative treatment with regimen DD-4A followed by nephrectomy + lymph node sampling and abdominal XRT	71% OS, 71% RFS
	DA	Immediate nephrectomy + lymph node sampling followed by abdominal XRT and regimen I	67% OS, 75% EFS
	DA (preoperative)	Preoperative treatment with regimen I followed by nephrectomy + lymph node sampling and abdominal XRT	53% OS, 46% EFS
IV	FH	Nephrectomy + lymph node sampling, followed by abdominal XRT, bilateral pulmonary XRT, and regimen DD-4A	86% OS, 76% RFS
	FA	Nephrectomy + lymph node sampling, followed by abdominal XRT, bilateral pulmonary XRT, and regimen DD-4A	72% OS, 61% EFS
	DA	Immediate nephrectomy + lymph node sampling followed by abdominal XRT, whole-lung XRT, and regimen I	33% OS, 33% EFS
	DA (preoperative)	Preoperative treatment with regimen I followed by nephrectomy + lymph node sampling, followed by abdominal XRT and whole-lung XRT	44% OS, 31% EFS
V	FH	Bilateral renal biopsies and staging of each kidney followed by preoperative treatment with regimen EE-4A (if disease in both kidneys stage II or less) or regimen DD-4A (if disease in both kidneys greater than stage II), followed by second-look surgery and possibly more chemotherapy and/or XRT	87% OS, 65% EFS
	FA	Bilateral renal biopsies and staging of each kidney followed by preoperative treatment with regimen I, followed by second-look surgery and possibly more chemotherapy and/or XRT	88% OS, 76% EFS
	DA	Bilateral renal biopsies and staging of each kidney followed by preoperative treatment with regimen I, followed by second-look surgery and possibly more chemotherapy and/or XRT	42% OS, 25% EFS

Abbreviations: FA, focal anaplasia; DA, diffuse anaplasia.

response to neoadjuvant chemotherapy, measured as a decrease in tumor volume, did not predict lymph node status at surgery.[127] Thus, tumor shrinkage with preoperative chemotherapy may not be reliably used as a criterion to indicate which patients will require adjuvant radiation. A subgroup analysis of those patients with stage II and III nonanaplastic Wilms' tumor aimed at determining factors associated with prognosis found that stage, tumor volume, and blastemal type histology are the most important prognostic factors.

The current SIOP 2001 study is evaluating risk stratification of patients for treatment based on postchemotherapy histologic findings.[60] SIOP now classifies tumors with complete necrosis as low risk and tumors with diffuse anaplasia and blastemal predominance after chemotherapy as high risk. Intermediate risk includes all other post-chemotherapy histologies.

United Kingdom Children's Cancer Study Group

The UKCCSG has also conducted trials of children with Wilms' tumor.[128–130] The UK approach is to biopsy the tumor prior to treatment. They have noted a 12% incidence of non-Wilms' tumor in patients with the typical features of Wilms' tumor on imaging study.[131] One percent of lesions were benign on biopsy, similar to rates found in SIOP studies.[124] The UKW1 and UKW2 studies evaluated the

single-agent VCR for treatment of stage I FH tumors.[129,132] The OS of 96% compares well with two-drug chemotherapy, but age of >4 years was considered an adverse prognostic factor.[130] The UKCCSG (1986–2001) treated stage I patients up to 16 years of age with immediate tumor resection and 10 weekly doses of VCR alone.[130] The 4-year EFS and OS for patients of >2–4 years old and >4 years were lower using single-agent VCR than those experienced by COG in NWTS-5, which used VCR with AMD.

Preoperative Chemotherapy versus Immediate Nephrectomy

A fundamentally different philosophical approach exists between the pediatric cancer cooperative groups. The NWTS and COG trials have relied on surgical and pathologic staging following up-front nephrectomy. Originally, this was driven by concern that staging information obtained following prenephrectomy chemotherapy may inadequately define the risk of relapse.[123] The value of this approach has been reinforced by the identification of molecular markers predictive of more aggressive disease.[52] On the other hand, preoperative treatment can produce dramatic reduction in the size of the primary tumor, decreasing the morbidity of surgery (Figure 32.7).[133] The specific advantages of this approach include a reduction in intraoperative tumor spill.[128] The SIOP and UK approach continue to use the histologic response of the tumor to preoperative therapy to decide postoperative treatment.

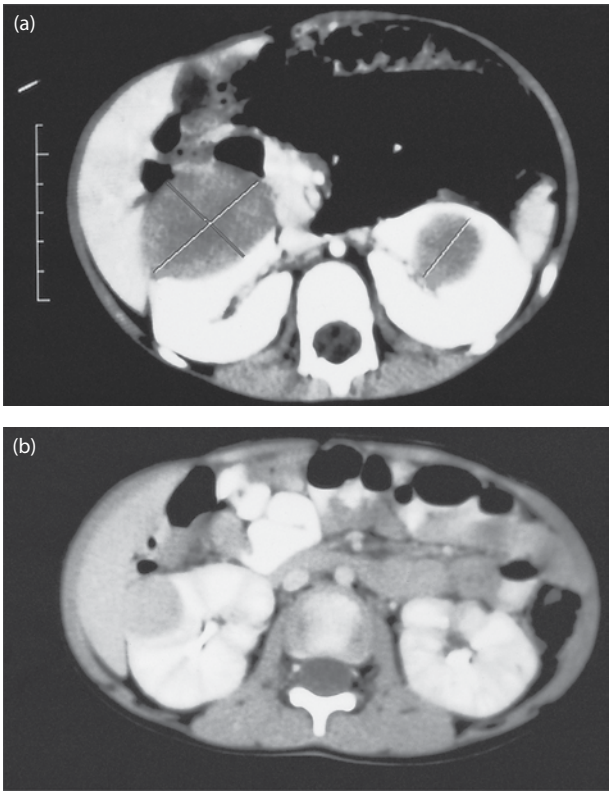

FIGURE 32.7 Computed tomography scan demonstrating bilateral Wilms' tumor: (a) before chemotherapy; (b) 6 weeks after chemotherapy, showing a marked reduction in the size of the masses.

In a departure from the standard up-front surgery approach, the current COG protocol for bilateral tumors, AREN0534, recommends up-front chemotherapy without pretreatment biopsy. Patients eligible for this protocol include those with bilateral tumors, those with tumors in a solitary kidney, and those with predisposing conditions.[134,135]

Both the COG and SIOP tumor staging systems are designed to stratify patients into low-risk and high-risk groups. The goal is to select out high-risk patients for more intense therapy, while minimizing treatment and thus morbidity for low-risk patients. Both groups want to reduce the number of patients receiving irradiation and DOX to avoid the late effects of treatment (see below). Currently, approximately 50% of SIOP patients are treated with an anthracycline and 17% undergo irradiation, whereas approximately 35% of NWTS and COG patients have historically received both therapies.[136–139]

Other indications for up-front chemotherapy in COG protocols include tumors inoperable at surgical exploration, and tumor extension into the IVC above the hepatic veins.[140–143] The latter two conditions are associated with an increased risk for surgical complications if primary nephrectomy is undertaken. Currently, it appears that up to 25% of patients eligible for primary nephrectomy undergo preoperative chemotherapy under COG protocols. It is presumed that these represent cases whereby tumors were large or concurrent metastatic disease existed in the face of a large tumor.

Special Considerations

Ureteral Extension

Wilms' tumor extension into the renal pelvis or even to the level of the bladder and urethra are rare but reported.[144–146] Ritchey et al. performed a thorough review of this subject, analyzing data from multiple NWTS studies, and concluded that the overall incidence was about 2%.[147] Roughly half of these children presented with gross hematuria; however, many with ureteral extension had nonspecific symptoms. Preoperative imaging detected only ~31% of cases, 49% were detected intraoperatively, and some cases were only detected on pathologic examination. The apparent insensitivity of preoperative imaging highlights the importance of intraoperative inspection by the surgeon in order to avoid inadvertently transecting tumor within the ureter. The authors recommended cystoscopy and retrograde studies for all patients presenting with hematuria, hydronephrosis, or a nonfunctioning kidney.[147]

Vascular Extension

Doppler ultrasound had been frequently used as an adjunct to CT for the detection of caval thrombus. A recent analysis of COG patients suggested that Doppler adds little value to this analysis and is not required.[148] For vena cava involvement below the level of the hepatic veins, the caval thrombus can be removed via cavotomy after proximal and distal vascular control is obtained. Generally, the thrombus will be free-floating, but if there is adherence of the thrombus to the caval wall, the thrombus can often be delivered with the passage of a Fogarty or Foley balloon

catheter. If the thrombus extends above the level of the hepatic veins, preoperative chemotherapy can shrink the tumor and thrombus, facilitating complete removal.[140,149] For cases extending into the atria, a combined approach involving cardiac surgeons is required (Figure 32.6). Nephrectomy is accomplished, and the patient is subsequently placed on bypass for clot removal.

Inoperable Tumor

With the exception of the current BWT protocol, current COG protocols continue to advocate for up-front surgery for the primary tumor. Under specific circumstances, however, deferred surgery is allowed. These cases are frequently referred to as "inoperable." Specific circumstances include tumor thrombus extending into the IVC above the level of the hepatics, tumors that involve contiguous structure and would require removal of adjacent organs, tumors that in the surgeon's opinion would expose the patient to unnecessary morbidity or mortality, and large tumors associated with a high risk of spillage, as well as patients with pulmonary compromise due to extensive pulmonary metastasis.[142] A tumor should not be judged inoperable based on imaging studies alone. Preoperative imaging can overestimate local tumor extension, so inoperability should only be determined on surgical exploration. It is also important to remember that the misdiagnosis rate of renal masses after assessment by diagnostic imaging is 5%.[124,131]

If a tumor is found to be unresectable, pretreatment with chemotherapy almost always reduces the bulk of the tumor and renders it resectable.[141,150] Patients who are staged by imaging studies alone are also at risk for understaging.[124] A patient determined to have an inoperable tumor should be considered stage III and treated accordingly.[141] Typically, repeat imaging is performed after 6 weeks of chemotherapy. Experience in SIOP has shown that maximal reduction in tumor volume occurs within the first 8 weeks.[124] After there has been adequate shrinkage of the tumor, definitive resection can be completed.

Partial Nephrectomy in Unilateral Tumors

Reports of successful renal preservation in BWT and, more recently, in unilateral Wilms' has prompted some centers to consider renal-sparing surgery for unilateral tumors (Figure 32.8).[151–154] Proponents of renal-sparing surgery for unilateral tumors will cite concerns about the late occurrence of renal dysfunction in children who have undergone unilateral nephrectomy. There is both clinical and experimental evidence of hyperfiltration damage of remnant nephrons after a loss of renal mass. Following treatment for unilateral Wilms' tumor, some patients develop proteinuria and a decrease in creatinine clearance.[155] Others have pointed to the increase in low-stage chronic kidney disease among survivors of unilateral nephrectomy.[156,157] Interest in this subject has also been sparked by adult literature identifying benefits related to cardiovascular health, bone health, and erectile function in patients undergoing partial nephrectomy as opposed to radical nephrectomy.[158–161] Review of NWTS patients found that the incidence of renal failure in children with unilateral tumors is 0.25%.[139] Most of those patients experiencing clinically significant renal dysfunction had

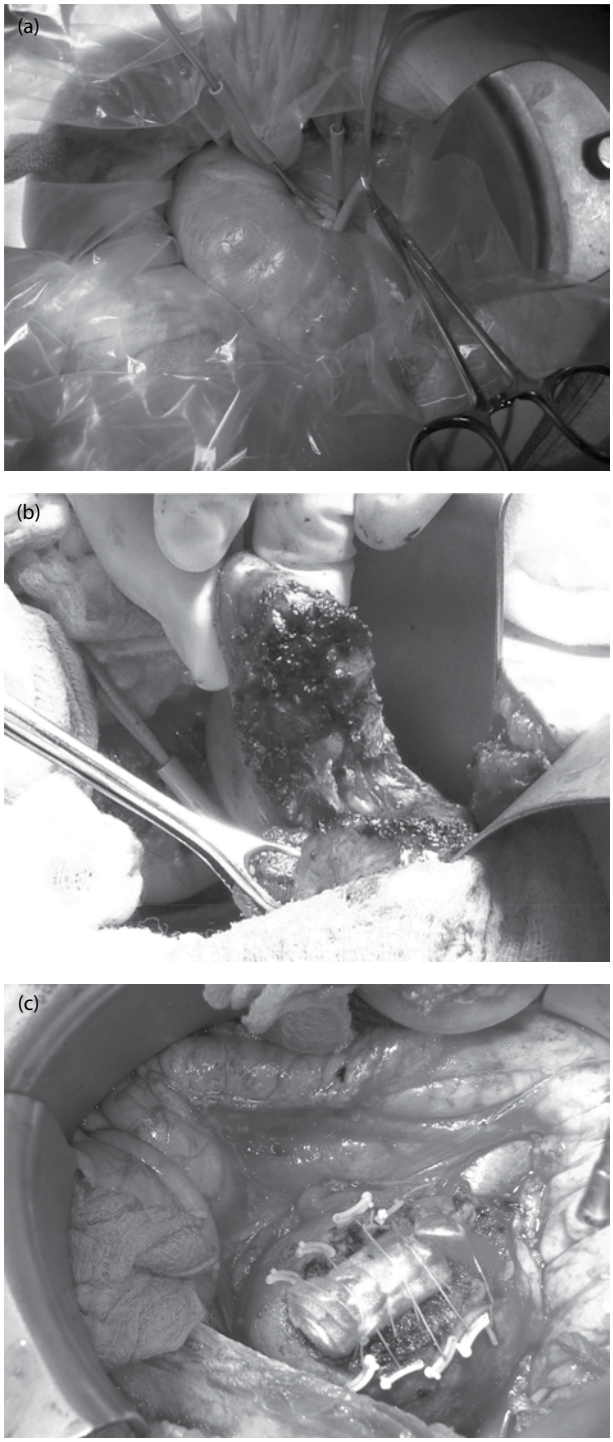

FIGURE 32.8 Intraoperative images of patient undergoing partial nephrectomy for renal mass. (a) Kidney is isolated in impermeable catch drape, and renal vascular has been isolated in preparation for clamping if needed. (b) Partial nephrectomy in progress. (c) Partial nephrectomy completed with gel foam with overlying bolsters.

DDS with intrinsic renal disease, which often progresses to end-stage disease even in the absence of tumor. More recently, other subgroups of patients at increased risk for renal insufficiency have been identified.[136] Patients with the WAGR syndrome have a markedly increased risk of

renal failure. Breslow et al. found a 38% risk of renal failure that occurred at a median of 14 years from diagnosis.[136] They also noted an increased risk for renal failure in children presenting with genitourinary anomalies and Wilms' tumor. This has resulted in current recommendations (AREN0534) that allow for renal-preserving surgery in unilateral syndromic patients at risk for recurrent Wilms' or renal dysfunction. Based on the overall low risk of renal failure in nonsyndromic patients with unilateral tumors, the official COG recommendation remains total nephrectomy.

The issue of cancer control related to partial nephrectomy is another significant consideration surrounded by intense debate. A review of children with BWT enrolled in NWTS-4 found that the incidence of local recurrence was 7.5% following partial nephrectomy and 14% after enucleation.[162] Although OS was comparable, patients with residual disease and recurrences required additional therapy to attain a similar outcome. Previous reports demonstrating poor outcomes for patients experiencing local recurrence have prompted concern regarding the application of partial nephrectomy to unilateral Wilms' patients.[106] However, a recent literature review focused on assessing oncologic outcomes of patients undergoing partial nephrectomy for unilateral Wilms' suggests that oncologic outcomes for selected patients undergoing partial nephrectomy are the same as those for patients undergoing radical nephrectomy.[154] A 2001–2009 SIOP study evaluated the groups' experience with partial nephrectomy for unilateral Wilms'. All patients were pretreated with chemotherapy, and a partial nephrectomy was performed in 91 (3%) of 2800 patients. The overall recurrence rate was 4%, but only one patient experienced local recurrence. The overall and local recurrence rates were comparable to those of the total nephrectomy patients, but the groups were not staged matched. Tumor rupture rates were similar, as were overall and EFS rates. These reports lend credence to the possibility of performing partial nephrectomy in selected unilateral Wilms' patients without compromising cancer outcomes. However, one must consider that in both of these reports a majority of patients had been pretreated with chemotherapy, which is not the current COG standard and can have a profound effect on local control and recurrence.

Owing to the typically large tumor size at presentation, the feasibility and applicability of partial nephrectomy to children with unilateral Wilms' are frequently questioned. A recent analysis performed by the COG looked at this question in very low-risk (<age 2, <550 g) unilateral Wilms' tumors. This population would seemingly be particularly technically amenable to partial nephrectomy as a result of smaller tumor size. Inclusion criteria required preservation of at least one-third of the kidney, in situ procedure performance, and absence of vascular involvement. Disappointingly, partial nephrectomy was deemed technically feasible in only 9% of patients based on radiologic assessment. This study highlights the limited number of eligible patients utilizing the COG up-front surgery approach. Whether this number can be increased by utilizing pretreatment strategies is unclear. In a recent SIOP analysis, only 3% of patients received partial nephrectomy—as of this writing, it is unclear if this implies technical feasibility in only 3% of cases. Conversely, substantial size reduction has been reported using pretreatment chemotherapy.

In summary, while the risk of developing renal failure following treatment appears to be quite low for most children with unilateral Wilms' tumor, continued long-term follow-up of this cohort of children is necessary. While emerging data suggest a potential long-term benefit to renal preservation in cases of solitary renal tumors, the cooperative groups have yet to do a large randomized trial. Finally, within the COG the opportunity to apply renal-sparing surgery to unilateral tumors may be limited due to a philosophical approach that favors up-front surgery.

Bilateral disease

Synchronous bilateral nephroblastoma occurs in about 5% of children with Wilms' tumor, with metachronous lesions developing in only 1% (Figure 32.4).[134,163,164] Therapy of children with BWT is directed toward preservation of renal parenchyma to avoid renal insufficiency.

A review of NWTS patients with BWT found that 9.1% of synchronous bilateral tumors and 18.8% of metachronous bilateral tumors have developed renal failure.[139] The most common etiology for renal failure was the need for bilateral nephrectomy for persistent or recurrent tumor in the remaining kidney after initial nephrectomy.

The initial management, therefore, is chemotherapy. Repeat imaging is done 6 weeks later to assess response of the tumors. Experience in SIOP has shown that maximal shrinkage occurs at about 6–8 weeks of chemotherapy. As noted above, one cannot predict the histology of the tumor by imaging response to the chemotherapy.[60,165] Differentiated tumors may show a poor clinical response to therapy, but have an excellent prognosis if the tumor is completely excised. Tumors with complete necrosis and predominantly regressive changes can also increase in size during therapy.[60] Tumors not responding to therapy require open biopsy to exclude anaplasia. At the time of the second-look procedure, partial nephrectomy or wedge excision of the tumor should be considered, but only if complete tumor resection with negative margins can be obtained, and part of either or both of the kidneys can be salvaged. If the tumors are not amenable to partial resections, patients with persistent viable tumor are then treated with a different chemotherapeutic regimen. The patient should be reassessed after an additional 12 weeks of chemotherapy to determine the feasibility of resection. If it appears that either or both of the kidneys can be salvaged, partial nephrectomies or wedge excisions of the tumors are performed. Radical nephrectomy is performed to remove the kidney with too extensive tumor involvement when only one of two can be preserved. Although rare, bilateral nephrectomies and dialysis may be required if the tumor fails to respond to chemotherapy and radiation therapy. The recommended interval between successful completion of treatment of the Wilms' tumor and renal transplantation varies. Some clinicians advocate a waiting period of 2 years to ensure that the patient does not develop metastatic disease; others have found that a 1-year interval is sufficient.[166] SIOP investigators have noted that late relapses have occurred in patients with BWT more

than 4 years posttreatment and recommended long-term follow-up.[163]

LATE EFFECTS OF TREATMENT

One of the major objectives of the pediatric cancer cooperative groups has been to reduce the intensity of treatment in order to prevent or lower the morbidity of multimodal therapy.[167] It is now well established that each therapeutic modality used in the management of Wilms' tumor can result in both acute and delayed toxicities affecting numerous organ systems. Late effects of cancer therapy are predictable and are based on treatment modalities used, age of patient at treatment, and time elapsed since therapy. Clinicians must be familiar with the spectrum of problems that face these children as they grow into adulthood. Young children are at particularly high risk for growth and development defects given their increased tissue sensitivity. Long-term follow-up of treatment-related complications has been an integral role of the NWTS and COG.

Children treated with radiation and chemotherapy for Wilms' tumor are at increased risk for second malignant neoplasms (SMNs). NWTS investigators reported that 15 years after initial (Wilms' tumor) diagnosis, the cumulative incidence of an SMN is 1.6% and increasing steadily.[168] This is more than eight times the expected incidence. The risk of developing leukemia or lymphoma is greatest in the first 8 years after treatment. The risk of developing a solid tumor continues to increase over time. Most tumors occur in previously irradiated areas, but prior treatment for relapse and use of DOX were also associated with an increased incidence of SMNs. Congestive heart failure is a known complication of treatment with an anthracycline,[169] and the frequency is directly proportional to the cumulative dose received. In addition to the acute cardiotoxicity, reports are surfacing of cardiac failure up to 20 years after treatment.[170] In a preliminary review of patients entered on NWTS-1, NWTS-2, and NWTS-3, the frequency of congestive heart failure was 1.7% among DOX-treated patients. The risk was increased if the patient received whole-lung irradiation. DOX has been shown to be a radiation sensitizer.[168] In light of these findings, all children who undergo treatment with these modalities should undergo periodic reevaluation.

Growth and development disturbances are well-established complications of cancer therapy in children. Spinal irradiation can result in severe reduction in spinal growth, as well as scoliosis.[171] Similarly, chemotherapeutic agents can have a direct effect on chondrocytes, resulting in resistance to endogenous growth hormone and subsequent growth impairment.[172] Hogeboom et al. studied the impact of treatment on stature in Wilms' tumor patients.[173] They concluded that while reductions in stature directly correlated to total radiation dose and age at treatment, currently recommended radiation doses should not result in a clinically significant impact.

Damage to reproductive systems can lead to problems with hormonal dysfunction and/or infertility. The gonads are particularly sensitive to radiation, and gonadal radiation in males can result in temporary azoospermia and hyogonadism.[174] The effect on the testis is dose related, and the prepubertal germ cells also appear to be radiosensitive. In a follow-up of 10 men treated for Wilms' tumor in childhood, oligospermia or azoospermia was found in 8.15. The Leydig cells are more radioresistant than the germ cells, but higher doses can produce damage resulting in inadequate production of testosterone. This can result in delayed sexual maturation. Chemotherapeutic agents can also interfere with testicular function, particularly alkylating agents. Acute toxicity with germ cell depletion occurs in all age groups. Some long-term studies suggested that prepubertal testes are resistant to chronic toxicity.[175] However, recent studies have indicated that prepubertal testes are not protected from chemotherapy-induced damage. One report found that 12 of 19 prepubertal males treated for a variety of solid tumors were sterile as a result of treatment.[176,177]

Female Wilms' tumor patients exposed to radiation are a risk for decreased fertility, intrauterine growth retardation, and spontaneous miscarriage in a dose-dependent fashion. In addition, females who received abdominal radiation have a 12% incidence of premature ovarian failure.[178] Of 16 women who received whole abdominal irradiation, all had evidence of ovarian failure, and 75% were amenorrheic.[179] Chemotherapy-induced damage to the ovaries is most often associated with alkylating agents. A decrease in the number of follicles is seen in prepubertal girls treated with chemotherapy.[180] Premature menopause is a common complication of female childhood cancer survivors, and is usually associated with radiation therapy and/or treatment with alkylating agents. Byrne et al. demonstrated that women receiving alkylating agents were 9.2 times more likely to enter premature menopause.[180,181] Although further studies are needed to assess the extent of the problem, it appears prudent to counsel survivors at risk that a delay in first pregnancy may preclude having children.[182] In the future, cryopreservation and reimplantation of oocytes may be a viable alternative for these patients.

Several studies have addressed the risk of pregnancy in survivors after childhood cancer therapy. As noted above, girls with Wilms' tumor appear to have a higher incidence of Müllerian anomalies, causing some authors to suggest postpubertal level 2 ultrasound evaluation to detect these abnormalities prior to pregnancy.[18] Women with prior abdominal radiation have the greatest potential for adverse pregnancy outcomes. In a study of patients treated for Wilms' tumor, an adverse outcome occurred in 3% among nonirradiated women compared with 30% of women who received abdominal irradiation.[183] Perinatal mortality rates are higher, and infants are more likely to have low birth weights. The potential mutagenic effects of anticancer therapy are of concern. Most studies have found no increase in the incidence of congenital anomalies and no cases of Wilms' tumor in the offspring of survivors.[183,184]

Renal impairment is rare, but possible, in nonsyndromic children undergoing nephrectomy for unilateral disease. Although nephron-sparing techniques are currently being utilized more frequently, most children treated for Wilms' tumor will undergo unilateral nephrectomy as part of the initial treatment. Renal dysfunction

as a late effect of treatment is a particular concern in patients treated for BWT. Sudour et al. found that 20% of bilateral patients treated with multimodality therapy in SIOP 93 experienced impaired renal function; some required hemodialysis or transplant.[185] A review of NWTS patients found that 9.1% of those with synchronous BWT eventually developed renal failure, and the majority of cases were due to second nephrectomy for persistent or recurrent tumor in the remaining kidney after initial nephrectomy.[139] In patients who do not undergo bilateral nephrectomy, impairment of renal function may be related to irradiation, administration of nephrotoxic chemotherapeutic agents, or hyperfiltration of the remaining nephrons. Initially, there is compensatory hypertrophy that develops in this kidney.[186,187] The data are conflicting regarding renal compensatory hypertrophy in patients who receive whole abdominal irradiation. Walker et al. found no difference in renal lengths between patients treated with chemotherapy and radiation versus chemotherapy alone.[187] However, a more recent report used ultrasound to calculate renal lengths and found that patients receiving radiation had poor compensatory growth.[186]

The kidney is sensitive to the effects of radiation. Radiation doses to the kidney should be limited to 12–15 Gy. Mitus and colleagues correlated functional impairment with the renal radiation dose in a review of 100 children treated for Wilms' tumor.[188] The incidence of impaired creatinine clearance was significantly greater for children receiving >12 Gy to the remaining kidney, and all cases of overt renal failure occurred in patients who had received >23 Gy. Clinical signs of radiation nephritis may occur very acutely or begin months or years after therapy is discontinued.[188] Direct radiation nephrotoxicity is the usual cause, with injury to the intrarenal vasculature.

Nephrotoxicity related to chemotherapy is well documented. Studies in children have demonstrated that alkylating agents in particular are associated with renal tubular dysfunction related to drug metabolites.[189] Unfortunately, Mesna has not been protective against these effects. A recent study by Bardi et al. has suggested that high-risk Wilms' patients receiving agents such as cyclophosphamide may be at risk for early, subclinical, renal dysfunction, as evidenced by elevated levels of cystatin C, a measure of glomerular function, and elevated *N*-acetyl-D-glucosaminidase, along with microalbuminuria.[190] The latter are both indicators of proximal tubular dysfunction. The long-term significance of these findings remains to be determined.

The liver may also be subject to long-term negative sequelae of Wilms' tumor therapy. A recent retrospective review of 158 patients from a single institution sought to determine the rate of hepatic veno-occlusive disease (VOD), now known as sinusoidal obstruction syndrome (SOS), that occurs in patients following preoperative chemotherapy with VCR and actinomycin.[191] Liver biopsy was performed after 4 or 8 weeks of chemotherapy, and 45.1% of patients had histologic evidence of VOD; the rate was highest in the group treated according to the SIOP 2001 protocol, where a single larger dose of actinomycin was given in comparison to smaller, repeated dosing.

OTHER RENAL TUMORS OF CHILDHOOD

Cystic Partially Differentiated Nephroblastoma

Cystic partially diffentiated nephroblastoma (CPDN) is a benign, solitary, cystic lesion, thought to be in the spectrum of nephroblastoma. The cysts are lined with blastemal or other immature elements. These lesions should not contain hemorrhage, necrosis, or calcification. Cysts are common in Wilms' tumor and range in size from microscopic to several centimeters in diameter. The majority of these lesions occur in the first year of life.[192] These lesions are indistinguishable radiographically from solitary multilocular cysts, described below. Surgery is curative in almost all patients, with recurrence the result of incomplete resection.[193,194]

Multilocular Cystic Nephroma

Multilocular cystic nephroma is another benign renal lesion in the spectrum of nephroblastoma. Also known as multilocular cyst, it has a bimodal age incidence. This tumor is distinguished by the finding of only *mature* cell types within the septa of the cyst wall, which should be free of any nodularity. Fifty percent of the multilocular cysts reported in the literature have been found in children younger than 4 years; boys predominate in a ratio of 2:1. The second peak incidence occurs in adults and, unlike the pediatric cases, usually in women.[195] Cystic nephromas are commonly found incidentally on radiographic studies, but may present as an abdominal mass found on routine physical examination. Whereas the majority of cases of multilocular cystic nephroma have been unilateral, there are rare reports of bilateral cases.[196] The gross appearance of the tumor is its most distinguishing feature. The cut surfaces reveal a well-circumscribed multilocular tumor composed of cysts ranging from several millimeters to several centimeters in the greatest diameters. The tumor is well encapsulated, compressing the surrounding renal parenchyma. It is cured by nephrectomy, but incomplete excision by partial nephrectomy has resulted in tumor recurrence. If partial nephrectomy is considered, frozen section is indicated to exclude cystic, partially differentiated nephroblastoma.[192]

Congenital Mesoblastic Nephroma

CMN is found virtually exclusively in infants, and is the most common renal tumor in infancy, with a mean age at diagnosis of 2 months. The typical presentation is a newborn with an abdominal mass, but in recent years, a number of cases have been recognized prenatally with polyhydramnios (Figure 32.9).[197–199] Tumor induction is postulated to occur at a time when the multipotent blastema is predominantly stromagenic.[200] The neoplasm is grossly indistinguishable from Wilms' tumor, but is microscopically distinct with two major histologic types: classic and cellular. In a small percentage of patients, these two cell types may coexist in a "mixed pattern." The

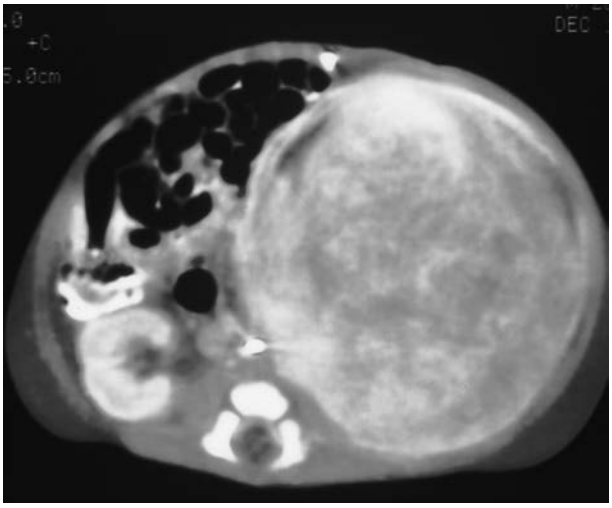

FIGURE 32.9 Computed tomography scan of an infant with congenital mesoblastic nephroma.

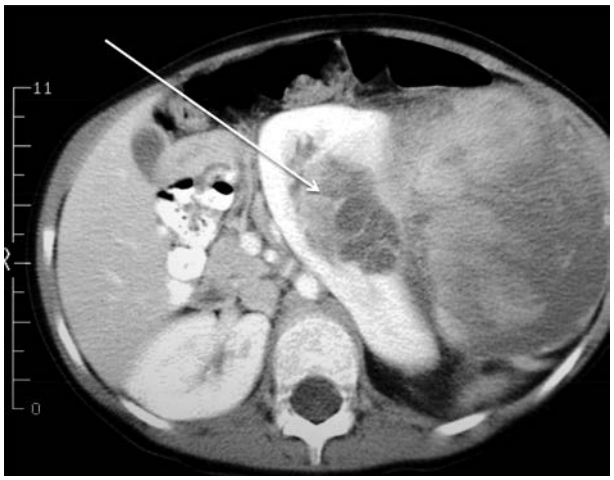

FIGURE 32.10 Image of patient with CCSK. Note the cystic component of the lesion (arrow).

classic subtype is characterized by interlacing sheets of bland spindle cells, and resembles infantile fibromatosis. Nodules of hyaline cartilage, thin-walled vascular spaces, and variable mitotic activity are often seen. The cellular variant has a solid sheetlike growth pattern, plump cells, and large nuclei frequent mitoses.[201–203] Unlike the classic variant, these lesions are well demarcated. This variant is virtually identical histologically to congenital fibrosarcoma. Molecular studies have found a similar translocation in both tumors that fuses the *ETV6* (*TEL*) gene from chromosome 12p13 with the chromosome 15q25 neurotrophin-3 receptor gene, *NTRK3*.[204] Imaging studies cannot reliably distinguish CMN from other renal mass lesions. Abdominal CT shows a heterogeneous solid mass arising from the kidney (Figure 32.6). Complete excision is curative for most patients with CMN.[197] Local recurrence and metastasis can occur, particularly with the cellular variant of CMN.[202,203] The pathology specimen will often identify extension of tumor into the hilar or perirenal soft tissue; therefore, complete surgical resection is important.[201] The risk of recurrence is thought to be less in children under 3 months of age at diagnosis, but metastases have been reported in a few infants.[205] Neither chemotherapy nor radiation therapy is routinely recommended, but consideration for adjuvant treatment should be given to patients with cellular variants that are incompletely resected. There are reports demonstrating the response of both inoperable and recurrent tumors to chemotherapy.[206,207]

Clear Cell Sarcoma of the Kidney

This tumor is also known as the "bone-metastasizing renal tumour of childhood" because of its predilection bony spread.[208] There is also an increased risk of brain metastases with this tumor.[209] CCSK accounts for 3.5% of renal tumors reported to the NWTS (Figure 32.10). This malignant mesenchymal tumor is made up of undifferentiated cells arranged into cords and nests.[69] Nuclei often appear "empty." Microscopically, the tumor subtly invades into surrounding normal parenchyma in sharp contrast to the borders of nephroblastoma. A number of variant patterns, such as myxoid, cellular, and epitheloid, may be present, hindering an immediate diagnosis. Unlike anaplastic Wilms' tumor, even stage I CCSK lesions are associated with increased rates of relapse. There are no reports of children with bilateral CCSK. Studies have demonstrated that the use of DOX is associated with a significant improvement in outcome for these children.[87,210] Patients with CCSK were treated on NWTS-5 with a regimen combining VCR, DOX, cyclophosphamide, and etoposide in an attempt to further improve the survival of this high-risk group. Preliminary analysis shows very promising results except for patients with stage IV disease. Seventy-nine patients with stage I–IV CCSK were treated with cyclophosphamide–etoposide, alternating with VCR– DOX–cyclophosphamide, and there have been 12 relapses, revealing a 77.6% 4-year RFS. Two-thirds of stage IV CCSK patients relapsed. Currently, one of AREN0231's protocol objectives is evaluating outcomes for a modified chemotherapy regimen based on prior results specifically for CCSK patients. Additionally, radiotherapy is being withheld for stage I patients who have done well with chemotherapy alone.

Rhabdoid Tumor of the Kidney

RTK was first identified by NWTS pathologists in 1978.[63] This highly malignant, rare renal neoplasm accounts for 1.6% of renal tumors registered to the NWTS.[211] It derives its name from the resemblance to rhabdomyoblasts, but it is not derived from myogenic cells; the cell of origin is unknown. Infants with RTK often have concurrent brain tumors. It is difficult to ascertain if these are metastases or two distinct primary tumors.[212] A unifying feature of these tumors, at renal or central nervous system sites, is the presence of mutation or deletion of the *INI-1* gene located at chromosome 22q11, which predisposes to the development of rhabdoid tumors.[69,212–214] This tumor is typically seen in infants and very young children, with a median age of 13 months. The prognosis of patients with rhabdoid tumor remains dismal with conventional chemotherapeutic regimens, with more than 80% of children dying within 1 year of diagnosis.[215] In NWTS-5, children with all stages

of rhabdoid tumor were treated with carboplatin, cyclophosphamide, and etoposide; they also received abdominal irradiation. Preliminary results again were poor, with survival ranging from 50% for stage I tumors to 21% for stage IV tumors, and an average survival of 25.8%.

Renal Cell Carcinoma

Only 5% of renal cell carcinomas occur in children.[216] These patients generally present after age 5 years, and it is the most common renal malignancy in the second decade of life.[217] Survival of children with renal cell carcinoma is dependent on the ability to completely resect the tumor. Raney et al. found that all children with stage I lesions survived.[218] Age is also a prognostic factor, with improved survival in children younger than 11 years. In contrast to adults with lymph node–positive disease, recent reports suggested that local lymph node involvement does not predict a poor outcome.[219] Renal cell carcinomas in children also differ in their histologic morphology and molecular characterization.[220] Currently, three main pathologic classifications in children exist: papillary renal cell carcinoma, renal medullary carcinoma, and renal cell carcinomas with clear cell features. There is a higher percentage of *TFE3* (transcription factor micro E3 binding protein) "translocation" carcinomas and "unclassified" carcinomas in the first two decades of life.[220] There is also a lower frequency of clear cell carcinomas and *VHL* (von Hippel–Lindau gene) alterations compared with adults. These tumors do not appear responsive to chemotherapy or radiation therapy. There currently is no unified grading or staging system, nor is there an accepted treatment protocol, for pediatric renal cell carcinoma.

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CHAPTER
33

Surgical Approaches for Pediatric and Adolescent Renal Tumors

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INTRODUCTION

Radical nephrectomy (RN) has traditionally been considered the basis of the surgical treatment of renal tumors in children and adolescents. The majority of the lessons learned about the management of pediatric renal tumors come from procedures to resect Wilms' tumors (WTs) or nephroblastoma. As described in Chapter 32, WT is the most common primary renal tumor in children, with an estimated annual incidence of 8.1 cases per million individuals and approximately 650 new cases in North America per year. It corresponds to 6% of all pediatric tumors and is the second most frequent intra-abdominal solid organ tumor found in children. Surgery alone is not sufficient for most children. In the early part of the last century, the survival rate with RN alone was poor (close to 30%). With the introduction of radiotherapy to the renal fossa in the 1940s, a decrease in local recurrence without a significant impact on the long-term survival was reported. Since then, the survival rate has improved dramatically thanks to the introduction of adjuvant chemotherapy and multimodal management, achieving survival rates greater than 90%.[1–5]

This significant progress in the treatment and understanding of patients with WT is the result of a multidisciplinary approach and multi-institutional cooperative group trials. In North America, patients with WT were managed according to protocols developed by the National Wilms Tumor Study Group (NWTSG) (now the Children's Oncology Group [COG]), which recommend primary nephrectomy with histological diagnostic confirmation for unilateral disease. In Europe, a different strategy is employed. Protocols developed by the International Society of Pediatric Oncology (SIOP) recommend initial treatment with preoperative chemotherapy, after radiographic diagnosis, followed by surgery afterwards. Despite these differences, oncologic outcomes remain comparable and excellent, irrespective of the utilized protocol.[6,7] In both, surgical resection is included and forms an integral part of management, differing mostly on the timing along the treatment course when it is performed.

Investigators have recently focused on reducing treatment morbidity while preserving survival in patients with low-risk tumors, by searching for novel therapies based on stage, histology, and genetic markers to improve outcomes in patients with high-risk disease.[8,9] Currently, therapy has been refined so that children with low-risk tumors may be spared intensive chemotherapy and radiation—with their long-term side effects. In patients with high-risk tumors, research continues to look for better options, including early treatment intensification. In addition, patients with bilateral disease and predisposition syndromes are being considered for nephron-sparing procedures, maximizing long-term renal function even in the setting of high-volume initial disease or high risk for metachronous lesions. Irrespective of the scenario, within the multidisciplinary treatment team the pediatric urologist or surgeon plays a critical role in the diagnosis and staging, and the surgeon's technical skills and judgment direct therapy and can have a clear impact on outcomes.[10,11] Thus, good surgical principles are paramount to adequate management and optimal cure rates.

ANATOMICAL RELATIONSHIPS OF THE KIDNEY

A good understanding of the retroperitoneum, as well as renal vascular anatomy, is important to adequately apply sound surgical principles for RN and partial nephrectomy (PN). The kidneys are located in the lumbar fossa, surrounded by a layer of perinephric fat, which is enveloped by a thin fascial layer (Gerota's fascia), the main anatomical boundary that helps define the area of resection during a RN and helps confine disease processes originating in the kidney.

The *perirenal space* is confined by Gerota's fascia (anteriorly) and Zuckerland's fascia (posteriorly), defining the anterior and posterior pararenal spaces. Recent studies based on perirenal abscess formation and distribution suggest that when large volumes of occupying fluid develop rapidly, the capacity to accommodate it within retroperitoneal spaces may be overwhelmed, resulting in disruption of these fascial planes. Spread may cross the midline (through the retromesenteric interfascial planes) or extend behind the kidney into Zuckerland's fascia, allowing for more extensive compromise of the posterior pararenal space and neighboring regions.[12] This can have clinical relevance and explain tumor spread to the posterior perirenal space in the presence of large or

FIGURE 33.1 Renal vascular anatomy on CT angiogram. Note the location and length of the main right (arrow) and left (arrow) renal arteries. Bilateral accessory renal branches are highlighted with open arrows.

ruptured renal masses, and challenges the perception that fascial layers are infallible robust barriers to neoplastic spread.

Other organs and structures adjacent to the kidneys should be kept in mind, as they are at risk for damage during surgical resection and serve as landmarks to guide dissection when the anatomy is significantly distorted by a large renal mass. These include

Posteriorly: Diaphragm, psoas major, and quadratus lumborum muscles

Anteriorly

Right kidney: Liver, hepatic flexure of the colon, second portion of the duodenum, adrenal gland

Left kidney: Spleen, tail and body of the pancreas, stomach, splenic flexure of the colon, adrenal gland

Renal Vasculature

The renal pedicle classically consists of a single artery and vein, which enter the kidney via the renal hilum. These structures branch from the aorta (just below the superior mesenteric artery) and inferior vena cava (IVC) at the level of the second lumbar vertebra. The vein is anterior to the artery, and the renal pelvis posterior to these vascular structures.

Arterial Blood Supply

The right renal artery leaves the aorta and courses with a caudal slope under the IVC toward the right kidney. The left renal artery has a shorter and more direct course, as it originates almost directly medially to the left kidney (Figure 33.1).

Upon approaching the kidney, at a variable distance from the ostium, the main renal artery splits into segmental branches (commonly apical or upper, middle, lower, and posterior). It is important to remember that these are segmental ("end") arteries, without collateral blood supply to their respective areas of irrigation, and that multiple renal arteries are sometimes encountered, separately perfusing different areas of the kidney (Figure 33.2). Ligation results in ischemia of the corresponding renal segment, which can be of value for selective embolization or control during nephron-sparing surgery, yet can adversely impact survival of important segments of parenchyma in the case of inadvertent damage during dissection. This is in contrast to the venous drainage, which does enjoy collateral drainage and tolerates segmental ligation without much consequence.

The kidney is susceptible to ischemia due to its very active aerobic metabolism. Although experimental studies indicate that a warm ischemia time of up to 30 minutes can be tolerated without significant functional loss, contemporary reports suggest that every minute counts.[13,14] Renal proximal tubular cells appear to be most sensitive, and may be damaged transiently or permanently, depending on the duration and severity of the injury. A focus during PN has been to develop strategies to minimize injury. "Zero ischemia" resection is based on anatomical vascular microdissection of tertiary and higher-order renal arterial branches. Only the tumor, with immediate peritumoral areas, is superselectively devascularized. Arterial

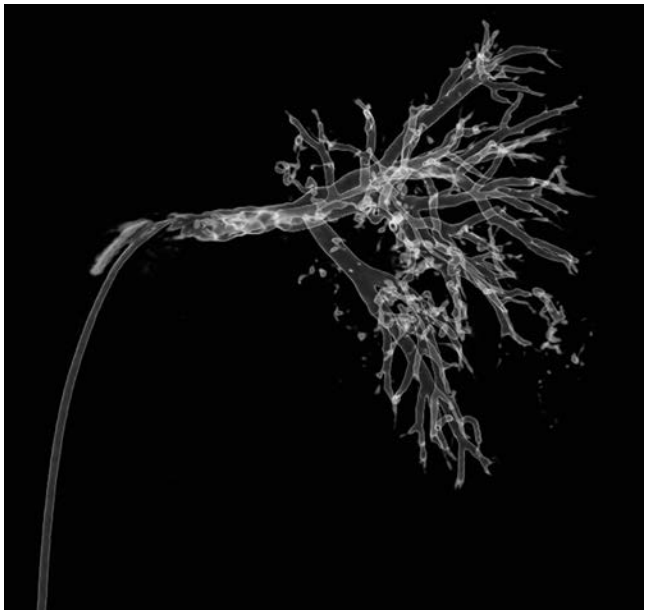

FIGURE 33.2 Selective renal arteriogram depicting selective perfusion of mid- and lower-pole segment.

FIGURE 33.3 CT scan demonstrating left renal vein pathway between the aorta and superior mesenteric artery (arrow), an anatomical position that explains the so-called "nutcracker phenomenon." Note the presence of an accessory renal vein (open arrow).

perfusion to the remainder of the parenchyma continues uninterrupted intraoperatively.[15] When a long surgical period of ischemia is expected, external surface cooling or perfusion of the kidneys with cold solution instilled into the renal artery is required. External surface cooling is the most practical and less invasive of the two methods. It is preferable to keep the entire kidney covered with ice for 10–15 minutes after arterial occlusion. Temperatures of 20°C–25°C can be maintained using this method. Studies have shown that hypothermia to this degree provides renal protection for up to 3 hours.[16] Generous preoperative and intraoperative hydration and avoidance of unnecessary renal artery manipulation or traction are additional measures. Administration of mannitol 10–15 minutes prior to arterial occlusion is also thought to be beneficial, as it increases renal plasma flow, decreases intrarenal vascular resistance, minimizes cellular edema, and promotes osmotic diuresis when renal circulation is reestablished.[17,18] When renal ischemia is necessary for surgery, it is preferable to occlude the artery alone since simultaneous occlusion of the artery and vein can produce venous congestion and additional renal damage.[17]

Venous Drainage

Renal venous drainage correlates closely with the arterial supply, yet multiple veins are less common. The right renal vein is shorter than the left and usually has no tributaries. The left renal vein is longer, travels between the aorta and superior mesenteric artery (Figure 33.3), and has a thicker muscular layer. These anatomical characteristics have a special surgical relevance in donor nephrectomy, as the left kidney is usually preferred due to its longer vein. Injuries to the right renal vein may also occur more easily given its thinner wall. Both renal veins enter the IVC on its lateral aspect, at about the same level, an anatomical relationship that is important because large tumors that compress the right renal vein and vena cava may lead to the intraoperative impression that the dissected renal vein is the right one when in reality it represents the left one (Figure 33.4). The left adrenal and gonadal veins are significant branches draining into the left renal vein, and

FIGURE 33.4 Left renal vein (arrow) encountered during dissection of the vena cava (open arrow) for large right renal mass. Due to anatomical distortion, it may be mistaken for the right renal vein and inadvertently ligated.

their presence has important implications for extensive vascular resections. Occlusion of the left renal vein at the level of the IVC is less likely to significantly impair venous drainage of the left kidney since collateral venous drainage can develop via tributaries, in contrast to a similar maneuver conducted on the right. Thus, special caution should be taken when performing dissection to keep adequate venous drainage of the right kidney.

IVC involvement by tumor thrombus has variable clinical repercussions depending on the side as well as the level of involvement. Lower extremity edema, an acquired varicocele, dilated superficial abdominal veins, proteinuria, pulmonary embolism, a right atrial mass, and nonfunction of the involved kidney are all clinical signs suggestive of intravascular tumor extension.[19] Transabdominal or transesophageal color Doppler ultrasonography and magnetic resonance imaging (MRI) are the preferred studies when evaluating for intravascular tumor extension.[20] In circumstances when the thrombus does involve the wall of the IVC, as seen in some cases after neoadjuvant chemotherapy, resection of the involved segment is required (Figure 33.5). Resection of the infrarenal segment of the IVC can sometimes be done relying on the presence of rich collateral circulation stimulated by the obstructing thrombus. With right-sided renal tumors, the suprarenal portion of the IVC may also be removed since venous drainage from the left kidney can occur via the gonadal and adrenal tributaries. Resection should not be performed when collateral venous circulation for the renal vein would be impaired, without alternate drainage.

Collecting System

The renal papillae constitute the first macroscopic structure of the renal collecting system. Each renal segment contains one or more major calyces draining the corresponding portion of the kidney. In total, 8–10 major calyces open into the renal pelvis. An understanding of the calyceal anatomy is required when performing PN to guarantee an adequate repair without compromising urine drainage. Preoperative placement of a ureteral stent may aid with detecting leaks and facilitate a watertight closure (Figure 33.6). Particular attention should be paid to cases of nephron-sparing surgery of tumors located near the hilum, due to the possibility of iatrogenic obstruction of

FIGURE 33.5 Vena cava replacement after removal of suprarenal segment with adherent tumor thrombus.

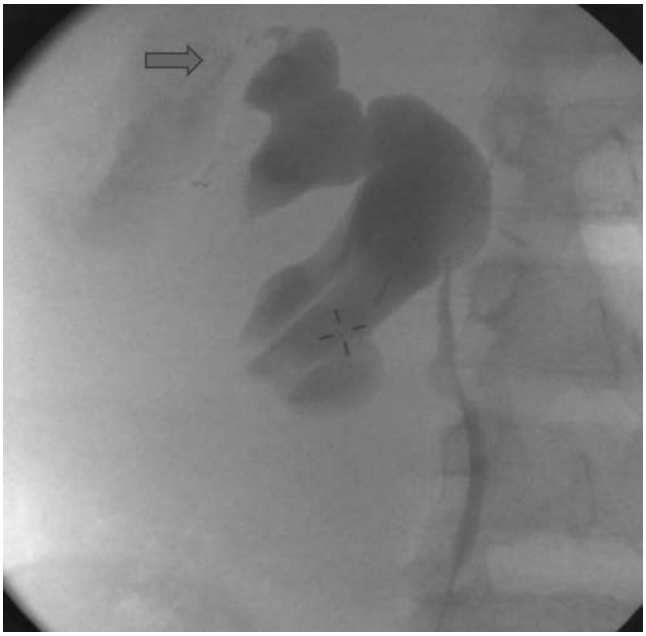

FIGURE 33.6 Extravasation (urine leak, arrow) after PN for small renal mass in patient with predisposition syndrome.

segments of the collecting system during attempted repair of a leak. In addition, the presence of a duplicated system should be kept in mind (Figure 33.7). This has obvious implications in terms of the blood supply to each moiety. The presence of this anatomical variant may allow for resection of part of the kidney (heminephrectomy) without compromising the drainage system of the other moiety.

IMPLICATIONS OF CLINICAL PRESENTATION

Most WT cases are diagnosed incidentally with a palpable abdominal mass (Figure 33.8). Gross hematuria and abdominal pain are less frequent findings at diagnosis. However, the presence of gross hematuria could indicate tumor extension into the collecting system,[21] so-called botryoid extension, a situation that should prompt total ureterectomy. As the tumors tend to be large, a generous incision is often required. In younger children and infants, a transverse abdominal incision may provide greater exposure, while in older patients a classic Chevron-type one is preferred.

Up to 25% of patients present with hypertension secondary to elevated plasma renin levels that resolves after removal of the tumor, 20% of children have hematuria, and 10% have coagulopathy, all findings that have important implications for safe anesthetic delivery and intraoperative management. Fever, anorexia, and weight loss rarely occur; their presence should raise the suspicion of another etiology (such as a neuroblastoma) or widely metastatic disease, both situations that may demand alternative management strategies than up-front nephrectomy. Tumor rupture and bleeding can cause an acute abdomen. In these cases, emergency surgical intervention may be

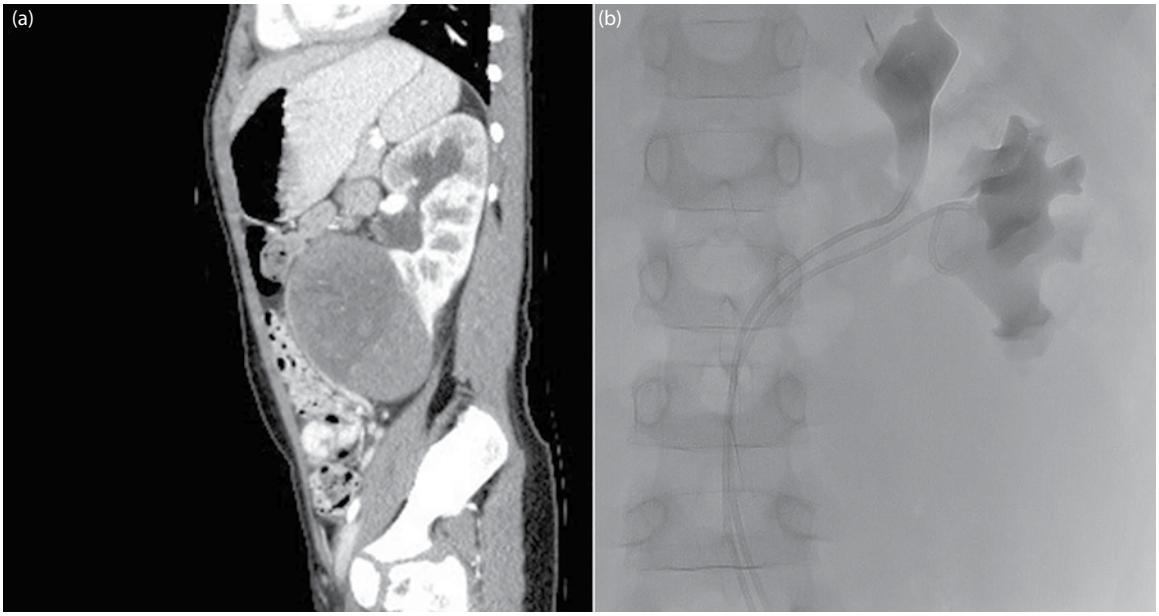

FIGURE 33.7 Lower-pole renal mass (a) on a patient with complete duplication, as documented during retrograde pyelogram and stent placement prior to neoadjuvant chemotherapy (b).

warranted, and the approach should be through a generous incision that allows good exposure and vascular control of the hilum, aorta, and vena cava, such as a large midline incision. Between 5% and 10% of tumors are bilateral, a presentation that can be synchronous or metachronous.[22] Bilateral tumors are more commonly found in children with predisposition syndromes (such as the Beckwith–Wiedemann syndrome); thus, the presence of bilateral masses should raise suspicion for such conditions and demands a thorough evaluation. The incidence of bilateral Wilms' tumor (BWT) demands neoadjuvant chemotherapy prior to surgical intervention[23] (Figure 33.9).

In 13%–28% of children, physical examination reveals congenital anomalies, such as aniridia, genitourinary malformation, hemihypertrophy, or signs of overgrowth.[24,25] Syndromes associated with an increased risk of developing WT include WAGR (aniridia, genitourinary malformation, and mental retardation), Beckwith–Wiedemann, and Denys-Drash syndromes. Other less common ones include isolated hemihypertrophy, Klippel–Trenaunay–Weber syndrome, and Perlman syndrome.[23] In all cases, the possibility of metachronous contralateral lesions should be kept in mind, and surgical management should focus on nephron- and adrenal-sparing procedures (if feasible). In addition, incisions should be fashioned in such a way that they may be used in the future if reinterventions are needed (i.e., new lesion or local recurrence at site of PN).

FIGURE 33.8 WT at presentation as a palpable renal mass.

IMPLICATIONS OF DIAGNOSTIC IMAGING FINDINGS

Any child with an intra-abdominal mass requires axial imaging in order to define the origin of the mass, the presence and involvement of the contralateral kidney, evidence of metastasis or rupture, and the presence of tumor thrombus.[26,27] The differential diagnosis of an intra-abdominal mass is extensive and includes other solid organ tumors, such as hepatoblastoma, neuroblastoma, germ cell tumors, and rhabdomyosarcoma. Abdominal ultrasound with vascular assessment of the renal vein and IVC should be the initial study. A computed tomography (CT) scan of the abdomen and pelvis with oral and intravenous contrast typically demonstrates an intrarenal neoplasm that displaces the collecting system and effaces the interface with the remaining normal renal parenchyma, a finding sometimes referred to as the claw sign (Figure 33.10). It is important to assess both kidneys to rule out bilateral tumors and the possibility of a renal mass in a solitary kidney. Current WT studies mandate radiographic imaging of the chest with CT scan, resulting in a high detection rate of lesions that would have been otherwise missed in the plain chest radiograph (Figure 33.11).[28,29] The presence of widely metastatic disease should raise concerns for pulmonary problems during or after surgery, and—in rare circumstances—favor the use of neoadjuvant chemotherapy

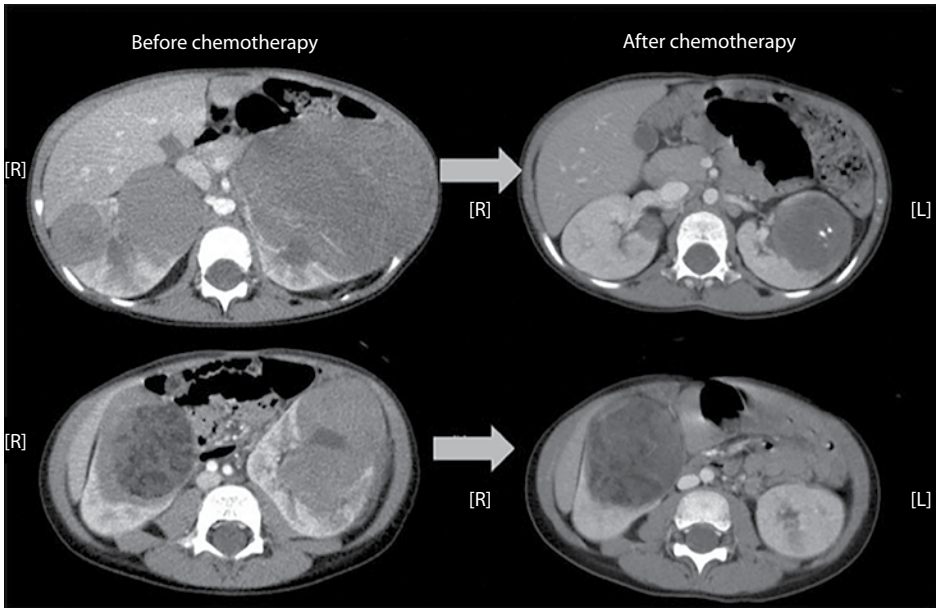

FIGURE 33.9 Response of BWTs to neoadjuvant chemotherapy.

FIGURE 33.10 CT scan findings on a patient with a large renal mass, confirmed as WT on pathology after RN.

before resection. Transabdominal or transesophageal Doppler ultrasound and echocardiography are the best methods to visualize the renal vein, IVC, and atrium in order to rule out vascular extension of the tumor, yet MRI provides exquisite assessment of venous structures and gives additional anatomical detail. Thus, in some centers the latter is the preferred imaging modality, a strategy that also avoids exposure to ionizing radiation. In addition, MRI may also be of value in distinguishing between nephrogenic rest and WT.[30]

Certain investigations are necessary only with specific types of tumors. Renal cell carcinoma (RCC) and clear cell sarcoma can metastasize to bone. Consequently, patients with focalizing musculoskeletal symptomatology should undergo a bone scan and skeletal survey prior to surgery.[31] In addition, brain metastases can occur with both clear cell sarcoma and rhabdoid tumor of the kidney; therefore, a head MRI or CT scan should be performed in these patients and obviously conducted preoperatively in

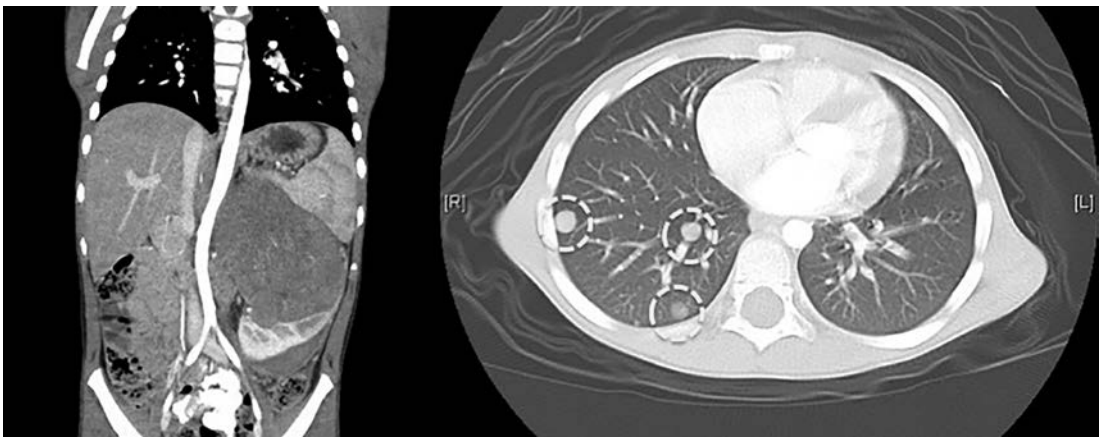

FIGURE 33.11 Pulmonary nodules in a patient with a WT (arrows). Lesions were not seen on admission plain chest x-ray.

any patient with focal neurological symptoms.[32] Although rare, both of these circumstances can have important implications in preparation for surgical management.

APPROACH FOR PATIENTS WITH SUSPECTED WILMS' TUMOR

Patient Preparation

In the absence of a preoperative biopsy, tumors in the first few years of life are approached with the assumption that they represent WTs. Adequate patient preparation and positioning are essential for an optimal surgical outcome. The surgical incision should allow the surgeon to have complete access to the tumor, gain adequate exposure for vascular control, accurately assess the abdomen (for staging purposes), and appropriately deal with potential complications, should they develop. Extension into the thoracic cavity, with a thoracoabdominal incision, is rarely used and is only recommended for large upper-pole tumors.

Placement of IV lines in the lower extremities should be avoided. This is particularly important when clamping of the vena cava is anticipated. Placement of an arterial line is recommended to accurately measure blood pressure in patients with hypertension, large tumors, or vascular involvement. In addition, consideration should be given to placement of an epidural catheter after induction in order to help with postoperative pain control.

Surgical Principles

Complete exploration of the abdomen is recommended, specifically examining for the presence of bloody peritoneal fluid (suggestive of tumor rupture), liver metastasis, and peritoneal seeding. Although WTs can be quite large, they typically displace rather than invade adjacent organs. This feature is key to understanding important principles: radical resection should rarely involve the removal of adjacent organs (except for the adrenal gland or small portions of fascia or muscle), and resectability should be determined in the operating room (and not solely based on imaging studies, with the notable exception of a large tumor thrombus or bilateral tumors).

Although in the past routine exploration of the contralateral kidney was considered mandatory, it is currently not performed or recommended if imaging (CT or MRI) is satisfactory and does not suggest a bilateral process.[10,26,27] Should the radiological evaluation raise suspicion for a possible contralateral synchronous lesion, management should shift to that of bilateral renal masses employing neoadjuvant chemotherapy with or without confirmatory renal biopsy. The implications of this particular aspect of care are not inconsequential, as RN with subsequent management of the contralateral lesion can lead to removal of valuable renal parenchyma, with increased risk for renal insufficiency. Lastly, any evidence of a tumor rupture should be clearly documented due to the increase risk for local recurrence and protocol-driven intensification of therapy (including radiation).[10]

Radical Nephrectomy

The colon is reflected to achieve adequate exposure and access to the respective great vessels (aorta on the left and vena cava on the right). On the left side, division of the splenocolic ligament facilitates this maneuver and avoids excessive traction and possible splenic injury. On the right side, the duodenum is also mobilized in order to avoid injury and provide access to the vena cava and hilum.

Initial ligation of the renal artery and vein should not be pursued if technically difficult, a situation commonly seen in the management of a large renal mass. In contrast to older recommendations, it is preferable to gently dissect and mobilize the kidney first to gain adequate exposure of the hilum. This is of greater importance when addressing a left renal mass, as the superior mesenteric artery can be in close anatomical proximity to the displaced hilum and erroneous ligation can have serious consequences. When the renal vein is exposed and controlled, it should be carefully palpated prior to ligation to rule out extension of the tumor into its wall or the lumen, irrespective of findings on imaging studies.[33] In the presence of a large right renal mass, the cava can be effaced and compressed against the tumor, increasing the risk of ligation by erroneously assuming it to be a dilated gonadal vein. Similarly, the contralateral (left) renal vein may be ligated by mistake. The right renal artery can be dissected either lateral to the vena cava or between the vena cava and aorta. This approach can be helpful with large tumors that extend medially. Tributaries (gonadal, adrenal, and lumbar veins) must be carefully dissected to avoid their inadvertent injury and intraoperative bleeding. In some cases, enlarged perihilar lymph nodes can add difficulty to the identification and exposure of the renal pedicle. In these cases, lymph node sampling before attempting to control the hilum is recommended.

Disruption of the renal capsule (by rupture, spill, or biopsy) upgrades the stage and often demands postoperative radiation. Thus, the kidney and tumor should be removed intact within Gerota's fascia, to ascertain any microscopic evidence of extension into the perinephric fat or positive margins. Similar to the growing body of evidence in adult oncological care, the adrenal gland should not be routinely removed, and can be safely preserved if it is not adherent to the tumor.[34] Ureteral ligation is routinely performed as distally as convenient, but complete resection of the ureter is not necessary except in cases with suspected urothelial extension (by either preoperative imaging studies, gross hematuria, or passage of tumor fragments through the urethra).

Slow, methodical separation of the mass from adjacent organs is almost always feasible and should be done patiently to avoid injury to other structures (such as the spleen, pancreas, liver, colon, and small bowel) or tumor rupture. Rarely is resection of a small portion of the liver, diaphragm, psoas muscle, or tail of pancreas warranted, and it should only be undertaken if it will allow for complete resection without additional operative morbidity. At times, this maneuver can be advantageous, avoiding upstaging due to positive margins and reducing the subsequent need for adjuvant therapy.[23,35] If complete resection is not possible, heroic measures should be avoided and a

tumor biopsy considered in anticipation of reexploration after chemotherapy (which decreases tumor size and stimulates development of a well-defined pseudocapsule around the tumor). Titanium clips are employed as markers for suspicious areas, resection margins, and residual tumor, in order to guide future radiological investigation or radiation planning.[10] Judicious use of clips before vascular control can be of great value, considering that placement of a vascular clamp across structures with clips may lead to suboptimal occlusion and bleeding.

Lymph Node Sampling

The presence of hilar and regional lymph node metastasis is an extremely important factor in staging.[36] Studies have shown that surgeons incorrectly identify histologically positive nodes as clinically negative 4%–11% of the time, and clinically positive nodes are negative up to 40% of the time. Therefore, routine sampling in the hilum and pericaval or para-aortic areas, along with any other suspicious nodes, is mandatory.[37,38] This is a sampling procedure, and not an extended lymph node dissection. Unfortunately, studies have also demonstrated a higher risk of recurrence in children who did not have their node status documented at the time of nephrectomy; thus, this aspect of surgical care should not be overlooked.[37,39]

Intravascular Invasion

Tumor extension into the renal vein, cava, and right atrium presents special surgical challenges.[33,40,41] Thankfully, many of these tumor extensions regress with preoperative chemotherapy, an approach favored in cases of suprahepatic involvement or bulky disease with complete occlusion of the suprarenal vena cava, or in the presence of a large component of an associated clot in the contralateral renal vein or infrarenal cava (Figure 33.12). In patients with shortness of breath, hypoxia, or hemodynamic instability, the possibility of a tumor thrombus embolism should be entertained and appropriately worked up before chemotherapy or surgery.

Tumor invasion into the renal vein and infrahepatic vena cava can be removed en bloc with the kidney with good vascular control and generous mobilization of the liver. Primary resection of a thrombus extending into the hepatics or into the atrium should be avoided.[33,40,41] Even after chemotherapy, adherence to the vein wall may develop or persist; thus, resection is not always straightforward and should be done with cardiovascular surgery backup. Intraoperative transesophageal echography can be of value in monitoring the thrombus during surgery, including any gains by dissection of the kidney and renal artery control, as well as assessing heart function in the setting of a suspected embolism. Control of the renal vein or cava above and below the tumor with vessel loops or vascular clamps is always necessary. Similarly, portal triad vascular flow may need to be temporarily occluded (Pringle maneuver) to decrease blood loss from the liver in selected cases with venotomy extension to or above the hepatic veins. Whenever possible, the tumor thrombus should not be transected, as this may result in residual disease or lead to embolization. After chemotherapy, a desmoplastic-type reaction may fix the thrombus to the vessel wall, making surgical extraction more difficult, and a large venotomy may be required (Figure 33.12). If after preoperative chemotherapy the tumor still extends above the hepatic veins, cardiopulmonary bypass may be needed. The kidney and abdominal tumor thrombus should be mobilized prior to administration of systemic heparin. After placing the child on bypass, the right atrium is opened and the tricuspid valve inspected. The tumor is removed from the heart above and below at the same time to prevent tumor embolism.[10]

FIGURE 33.12 Large renal mass with tumor thrombus extending above the hepatic veins.

Tumor Spillage and Rupture

The resection technique can play an important role in determining subsequent adjuvant therapy.[30,35,36] Studies have consistently shown an increased risk of recurrence in patients with tumor spills or ruptures regardless of the cause, which can adversely impact survival. These events also result in intensification of adjuvant therapy with its associated consequences. Spillage—defined as transgression of the tumor capsule during operative removal, whether accidental, unavoidable, or by design—can be minimized with careful, gentle tumor handling. A spill would also occur if the surgeon transects the renal vein or ureter at the site of tumor extension. Percutaneous or open-needle biopsies are also considered local spillage, unless the peritoneal cavity has been grossly contaminated in the process.

Rupture refers to either the spontaneous or posttraumatic preoperative tumor breach with subsequent dissemination of neoplastic cells into the retroperitoneum and/or the peritoneal cavity (Figure 33.13). The finding of bloody peritoneal fluid is considered a sign of generalized abdominal soilage. When a hematoma is present, it is presumed

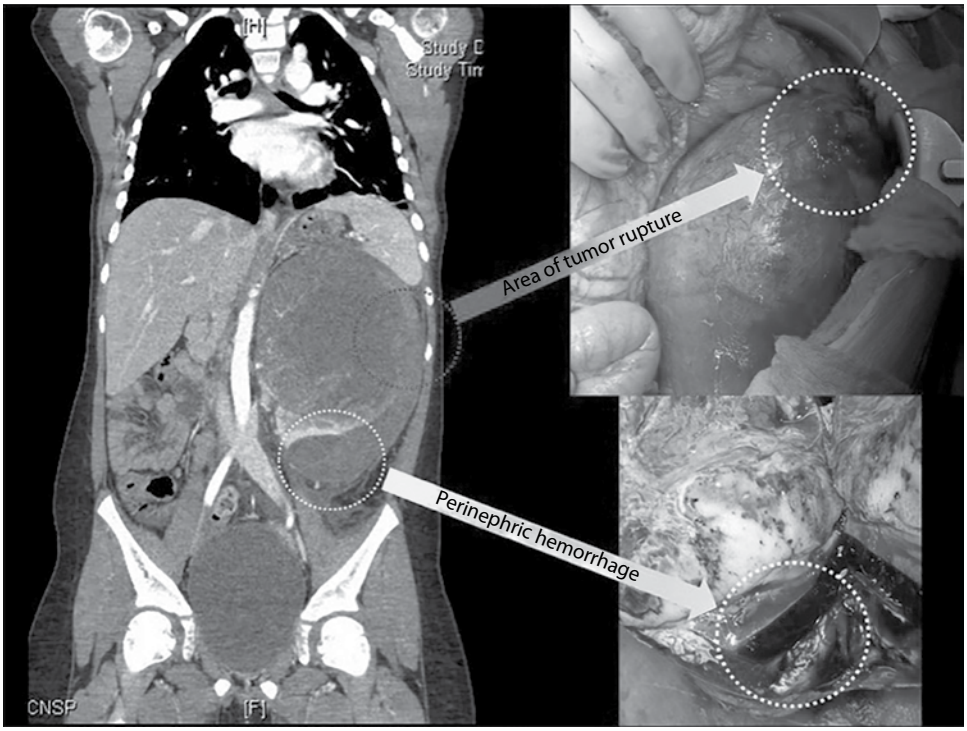

FIGURE 33.13 Renal tumor with preoperative imaging evidence of rupture.

that tumor cells are present in it, and the risk of contamination increases, particularly if the hematoma is entered or disrupted during dissection. Major soilage is also considered when the tumor penetrates the kidney capsule and the overlying peritoneum, with neoplastic tissue surface being in free communication with the peritoneal cavity. Separate, distinct nodules of tumor on the peritoneal or serosal surfaces, at a distance from the primary neoplasm, so-called "satellite implants," are also considered a sign of prior dissemination.[10] At the time of surgery, such lesions should be biopsied or removed, depending on the location, size, and involvement of adjacent structures.

Synchronous Bilateral Tumors and Conditions at Risk for Metachronous Lesions

In children with bilateral tumors (stage V) at the time of diagnosis, survival without early development of renal insufficiency has improved, with a focus on sparing renal parenchyma.[42] Unfortunately, renal failure has been described in 9.1% of these children.[43] Avoiding RN is recommended.[42] Primary excision of large tumor masses should also be discouraged unless absolutely necessary, such as in the case of rupture and persistent bleeding.

After initial chemotherapy, the patient is reassessed with axial imaging studies at 6 weeks. If imaging suggests that PN is feasible, it is reasonable to proceed with surgical exploration; otherwise, the process is repeated at 12 weeks. The goal, whether at week 6 or 12, is to accomplish complete resection of tumor with negative margins while preserving the greatest amount of viable kidney. However, surgery should not be delayed past 12–16 weeks to limit the risk of chemoresistant clonal expansion and avoid futile additive exposure to chemotherapy with little further gains in size reduction. A good response is associated with pathological improvement in terms of size regression, development of a pseudocapsule between normal parenchyma and tumor, and a more favorable consistency. Biopsies remain crucial for patients that do not appear to be responding to chemotherapy, since—aside from anaplastic lesions—tumors with complete necrosis and chemoresistant predominant histology can increase in size during therapy. Despite the apparent poor clinical and radiological response, differentiation of the tumor after chemotherapy has also been reported. Stromal and epithelial predominant tumors are often seen after chemotherapy, with reasonable prognosis as long as the tumor is completely excised.[10,23] In nonresponding tumors, concerns over undiagnosed anaplasia are always present.[44] Anaplastic tumors are less likely to respond to standard chemotherapy, thus making surgical resection more challenging. Due to the prognostic and chemotherapy resistance implications, any surgical procedure in patients with suspected anaplasia must ensure complete resection of the tumor, and complete (radical) nephrectomy is sometimes advocated in these cases.

A similar approach is commonly employed in children with a higher risk of metachronous renal tumors, such as patients with predisposition syndromes (including aniridia and overgrowth syndromes, like Beckwith–Wiedemann syndrome and idiopathic hemihypertrophy[45]). The concept of nephron-sparing procedures is identical to that for cases with synchronous lesions. Nevertheless, lesions are often smaller and not always managed with preoperative chemotherapy due to their size (detected with screening ultrasounds if the predisposition syndrome diagnosis

predates development of the renal neoplasm) and the possibility that the finding may represent a nephrogenic rest and not a WT.

Despite efforts to save functional renal parenchyma, some children will progress or develop end-stage renal disease soon after attempted surgical management of BWT (or renal tumors in a solitary kidney). In these cases, it is recommended to wait 2 years before renal transplantation.[46] When renal transplantation is considered, evaluation should take into account any vascular involvement and radiation fields, to maximize the chances of allograft anastomosis in a favorable location. Similarly, due consideration should be given to remove all native renal tissue prior to transplantation.

Partial Nephrectomy or Nephron-Sparing Resection

Following the successful introduction of nephron-sparing surgical techniques in adults with RCC, the concept has been introduced in the pediatric arena, currently favored in cases of bilateral neoplasms, solitary kidney, poorly functioning contralateral kidney, preoperative renal insufficiency, and predisposition syndromes. This shift has occurred with the aim to reduce the incidence or delay the development of renal insufficiency, which can have important implications in terms of morbidity and mortality during long-term follow-up.[43] Thus, the need for RN should always be questioned in patients with unilateral disease, and attention should be paid to rule out conditions at risk for contralateral tumors (i.e., aniridia, Beckwith–Wiedemann syndrome, and hemihypertrophy[47,48]) before rushing to surgery associated with the removal of valuable functional renal parenchyma.

Technical aspects are key to good surgical and oncological outcomes. Generous pre- and perioperative hydration is useful to optimize renal perfusion and decrease prerenal compromise due to relative volume depletion. In addition, the use of mannitol (given intravenously 5–10 minutes before renal artery occlusion) may help ameliorate ischemic renal damage. Whenever possible, resection should be done without clamping the renal artery (zero ischemia) or with selective occlusion of branches perfusing only the tumor area. In most cases, systemic anticoagulation is not necessary, and may increase the risk of bleeding during or after surgery. Even though laparoscopy or robotic or flank incisions are often favored in adults, pediatric cases are still done through an open transperitoneal approach. After opening Gerota's fascia, the kidney is elevated on its vascular pedicle. The perirenal fat overlying the tumor is left adherent and intact, and removed with the lesion. Use of intraoperative ultrasound is helpful to define small lesions or endophytic tumors, and can help define margins of resection, as well as proximity to large vessels or the collecting system. Once the lesions to be excised are identified, capsular incision limits are outlined with electrocautery. A thin rim of normal-appearing parenchyma should be included. Large vessels are controlled with absorbable sutures as the dissection progresses. Hemostasis along the parenchymal surface is then completed with argon beam coagulation and hemostatic agents (Figure 33.14).

Intrarenal surgery benefits from good hemostasis and a relatively bloodless field, conditions that sometimes

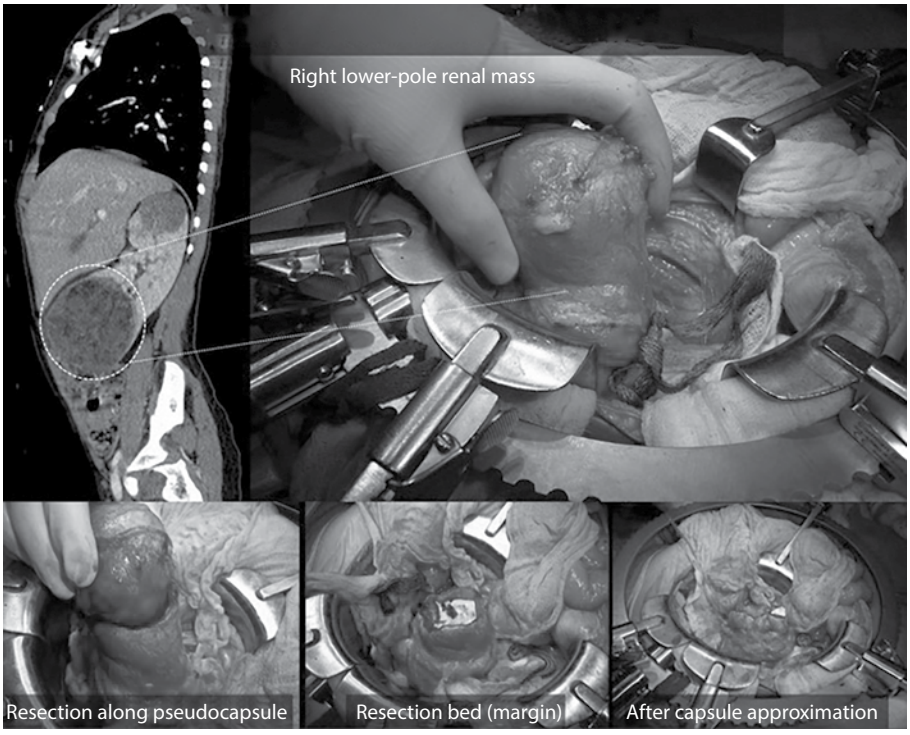

FIGURE 33.14 PN (nephron-sparing surgery) in a patient with bilateral renal masses. Resection of residual large lower-pole mass following neoadjuvant chemotherapy.

demand temporal occlusion of the renal pedicle. Clamping under normothermia provides a reasonable safe period of warm ischemia for approximately 20–30 minutes. If longer time is expected, ischemia tolerance can be prolonged with surface cooling using ice slush, understanding that there is a time-dependent risk of irreversible necrosis. In situ cold perfusion is an alternative that has been used in patients with multifocal BWT.[49] The interval of renal protection is similar to that obtained by surface cooling with slush; however, the arteriotomy and the venotomy used for continuous perfusion increase the risk of subsequent thrombosis. Digital compression of the renal parenchyma proximal to the line of resection often achieves satisfactory hemostasis, obviating the need for vascular occlusion. Irrespective of the technique employed, the renal vascular pedicle should always be encircled with vessel loops to provide rapid access and clamping in the setting of significant or difficult-to-control hemorrhage.[48]

The collecting system may be entered during resection. Identification can be aided by retrograde instillation with methylene blue (via a ureteral stent or by direct puncture into the renal pelvis). Once the opening is defined, it should be closed in a watertight, tension-free fashion with absorbable sutures. The decision to place an indwelling ureteral stent is based on the degree of disruption of the collecting system and the complexity of its closure, with a tendency to favor using one. Additional control can then be obtained by folding the kidney over the cut surface, using Surgicel® or another hematostatic agent over the raw surface. If excessive tension is noted during this maneuver, omentum or Gerota's fascia with perinephric fat can be used to bridge the defect. A closed suction drain is placed near the area of repair and generally removed before patient discharge, at least a day or two after removing the indwelling Foley catheter. Internal stents are removed cystoscopically 2–4 weeks later, taking into account postoperative adjuvant treatment protocols.[50]

Multiple frozen sections of the tumor margins should be obtained to verify that the resection extent is adequate. An additional slice of renal tissue may be resected if the margins are not clear, again with the aid of intraoperative ultrasound.[51] Oftentimes, it is difficult to differentiate resection from enucleation, which involves circumferential dissection along the pseudocapsule surrounding the tumor. This provides an easier plane for blunt dissection, with the advantage of increasing the ability to remove multiple tumors with maximum preservation of normal renal parenchyma and limited bleeding, at the expense of missing tumor penetration past the pseudocapsule.[52] This strategy increases the risk of entering the tumor and creating local spillage, resulting in upstaging.[53] If anaplasia is diagnosed before, during, or after the operation, in absence of clear margins, excision of the whole kidney is favored. As previously mentioned, some argue that anaplasia is an indication for RN irrespective of the margin status, and a relative contraindication for nephron-sparing surgery. This is debatable, yet an understandable approach considering the adverse impact anaplasia has on prognosis.

A baseline ultrasound of the kidney should be obtained within the first 2 weeks postoperatively. A recommended 1-year follow-up includes clinical examination and abdominal ultrasound monthly, chest x-ray every 3 months, and CT or MRI every 6 months.[53] At follow-up, the differential function of each kidney can be assessed by DMSA.[48]

PEDIATRIC RENAL CELL CARCINOMA

Clinical Presentation

RCC is relatively rare in children, representing less than 0.1% of all malignancies and 2%–6% of all renal tumors. It becomes more common in older children and adolescents (mean age 9–10 years).[54,55] Evidence suggests that pediatric RCC may be a different entity from adult counterparts, with distinct morphologic characteristics and unique genetic abnormalities. Childhood RCCs are more frequently papillary[56] and associated with Xp11.2 or TFE3 translocation.[55,57]

Patients often present with gross hematuria, flank pain, and/or a palpable mass, although about 12% of patients are asymptomatic, with the tumor detected incidentally by imaging.[58] RCC can be associated with important predisposition syndromes, such as von Hippel–Lindau, in which the tumors tend to be bilateral, associated with renal cysts, and prone to metachronous recurrences.[59,60] Survival is impacted by stage at presentation and completeness of resection, with an overall survival of 64%–87%.[55,61] More specifically, the 5-year survival is higher than 90% for stage I disease, 85% for stage II, 73% for stage III, and about 14% for stage IV.[62]

Imaging

A CT scan or MRI usually shows a solid renal lesion with variable enhancement. Heterogeneous areas of hemorrhage and necrosis may be present. There is a higher frequency of calcification in RCC (25%) than in WT (9%).[59]

Treatment

Therapeutic strategies for pediatric RCC have been extrapolated from the adult literature. Retrospective and observational data indicate that following adult protocols is reasonable, as doing so provides acceptable morbidity and overall survival.[61] Nephrectomy alone is adequate for stages I and II, with great outcomes with complete resection.[61,63] Also following trends in adult literature, nephron-sparing surgery has been considered for these patients. Cook et al.[64] reported excellent outcomes in patients who underwent nephron-sparing surgery for stage I or II, less than 4 cm RCC with 100% disease-free and overall 5-year survival.

The surgical technique for both RN and PN follows the steps described previously in this chapter. Importantly, though, is the increasing comfort with alternative approaches, such as flank (extraperitoneal) incision or minimally invasive (laparoscopic or robotic) options.

Treatment of metastatic disease is challenging because the tumor, as in adult counterparts, is poorly responsive to radiotherapy and there are limited chemotherapeutic regimens with modest benefit.[55] In very selected patients with obvious metastatic disease, there may be benefit in performing cytoreductive nephrectomy.[65,66] Currently,

part of the standard of care for metastatic RCC in adults involves the use of tyrosine kinase inhibitors (TKIs) and targets of vascular endothelial growth factor receptors, a trend that has expanded into the adolescent and pediatric practice.[55,58,61,67,68]

Laparoscopic Nephrectomy

In the past few decades laparoscopic radical nephrectomy (LN) has become the standard of care for localized renal tumors in adults, when PN is not feasible.[69,70] In children, however, the role of LN for renal masses has not been clearly defined. As WTs usually present with a large, friable palpable mass, offering laparoscopic resection (without preoperative chemotherapy) has been hampered by concerns over tumor rupture. Duarte et al., in 2004, published the first report of LN, showing feasibility and safety after chemotherapy.[71] Following this, several case series have been published, concluding that LN is reasonable, with no short-term adverse oncological results and the advantage of a shorter hospital stay and improved cosmesis.[72,73] Romao et al.[74] presented a series comparing the outcome of LN with RN in the management of renal tumors. Only six patients had preoperative chemotherapy (2 of 13 in the LN group vs. 4 of 32 for RN). They concluded that LN is an alternative to RN in well-selected cases of renal tumors, especially for small lesions or older children. As the age of the patient increases, and they enter adolescence, a stronger case can be made for minimally invasive options, following the aforementioned trends in adult cases (with predominant RCCs). Ultimately, multicentric prospective studies with longer follow-up are mandatory to confirm oncological outcomes similar to those of conventional open RN.

Surgical Technique

The patient is positioned in a semilateral position (30°). A semilunar umbilical incision is performed to gain access to the abdominal cavity following a modified Hasson technique.[75] A 5–10 mm trocar is placed and pneumoperitoneum is obtained using CO_2 to a pressure of 10–12 mm Hg. Using a 30° camera, the peritoneal cavity is examined. Two accessory trocars are placed: the first (10 mm) near the ipsilateral iliac fossa, and the second (5 mm) subcostally at the anterior axillary line. A third (5 mm) additional trocar can be placed near the xyphoid to help with the spleen or liver retraction.

Following similar surgical principles as in open surgery, the colon is mobilized medially to gain access to the retroperitoneum. Carefully, the anterior surface of the kidney is dissected off from the peritoneum layer. The ureter is then identified over the psoas muscle. Using blunt dissection, the ureter is lifted up, developing the posterior plane between the psoas and Gerota's. This maneuver facilitates identification and dissection of the renal hilum. At this point, the renal vessels are bluntly dissected; a suction irrigator is usually helpful for this step. The artery and vein are individually ligated, clipped, or controlled with a laparoscopic vascular stapler. After vascular control has been achieved, dissection of the upper pole is accomplished with sparing of the adrenal, if possible. Following complete mobilization of the kidney, the ureter is clamped and sectioned. Lymph node sampling is then completed; the specimens are placed in a plastic bag introduced through the 10 mm accessory trocar. The intact bag with the kidney and lymph nodes is then removed through a Pfannestiel incision.

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CHAPTER
34

Upper Urinary Tract Trauma

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SIMILARITIES AND DIFFERENCES IN EVALUATING PEDIATRIC VERSUS ADULT TRAUMATIC INJURIES

General Comments

Whether the incidence of renal injury following blunt abdominal trauma is increased in the pediatric compared with the adult patient population is controversial.[1–4] Hypothetically, the pediatric kidney is believed to be more susceptible to trauma due to a decrease in the physical renal protective mechanisms found in childhood, namely, a slightly lower renal position in the abdomen, an immature thoracic cage, and weaker abdominal musculature. Statistical evaluations to confirm that children have an increased risk of renal injury have revealed mixed results, and the question remains unresolved.[1–5] Overall, though, children appear to have nearly twice the incidence of renovascular injury than adults.[1] Additionally, preexisting congenital renal abnormalities are found three to five times more often in pediatric patients undergoing a screening CT scan for trauma than in the adult population.[2–4,6] *Classically, patients with a preexisting genitourinary (GU) abnormality present with a history of hematuria disproportionate to the severity of trauma*. In the pediatric population, the most common preexisting GU anomalies found, listed in decreasing frequency, are ureteropelvic junction (UPJ) obstruction, hydroureteronephrosis secondary to reflux, horseshoe kidney, nonobstructing–nonrefluxing hydronephrosis or hydroureteronephrosis, and primary obstructing megaureter.[2–4]

Traumatic-Induced Hematuria

In children, hematuria is unreliable in determining the extent of renal injury; some studies have failed to find any evidence of either gross or microscopic hematuria in up to 70% of children sustaining renal injuries grade 2 or higher. (For grading of renal injuries, see Table 34.1.) Microscopic hematuria has been reported to have a sensitivity and specificity of only 59% and 14%, respectively; the positive predictive value of gross hematuria has been found to be as low as 18%.[7] In essence, posttraumatic hematuria cannot be used as the sole determinant in deciding whether to begin the workup for renal injury.[8,9]

Indications for Imaging the Genitourinary Tract Following Trauma

In the adult, radiographic assessment of the GU tract is recommended following all penetrating trauma, as well as blunt trauma victims that fit one of the following criteria:

1. A significant deceleration (motor vehicle accident [MVA], fall from >15 feet) or high-velocity injury (strike to the back or flank with a high-velocity foreign object, i.e., football helmet, baseball bat, etc.)
2. Significant external trauma resulting in fractures of the thoracic bony structures, spine, pelvis, and femur; bruising of the torso or perineum; and/or signs of peritoneal irritation
3. Gross hematuria
4. Microscopic hematuria (>50 red blood cells per high-power field) associated with shock (systolic blood pressure less than 90 mmHg)[4,10–13]

Clinicians debate about whether the adult screening criteria outlined above apply to children.[7,8,11,14–18] This controversy is based on three separate concerns. First, hypotension in children is not a reliable indicator of the severity of injury. *Children often have normal blood pressure in spite of significant blood loss*. In children, serial hemoglobin determination is a better assessment of blood loss than hypotension.[15] Second, there is no consensus opinion in the literature regarding the definition of an associated injury in the child. For example, pediatric trauma clinicians have not established whether an isolated closed-head injury indicates the need for a screening abdominal computerized tomogram (CT).[8] Finally, there is no standard definition of a deceleration or high-velocity injury, with some authors neglecting to include the latter criteria in their list of indications for abdominal three-dimensional imaging. Despite these discrepancies, though, Santucci and colleagues determined that adult screening criteria are still useful in children and should be used to work up children for renal injury following trauma.[11]

RADIOGRAPHIC AND ENDOSCOPIC ASSESSMENT AND TREATMENT OF GENITOURINARY INJURIES

Abdominal and Pelvic CT and Single-Shot IVP

The patient's hemodynamic stability determines whether, when, and occasionally what type of imaging studies should be done. *In the clinically stable patient, a triphasic abdominal and pelvic CT scan (precontrast study, followed by a study immediately after injection of contrast and then a 15- to 20-minute delayed study) is the most sensitive method for diagnosis and classification of GU trauma*. See Table 34.1 for classification of renal trauma.[4,8,9,11,12,16,17]

In the clinically unstable patient, a single-phase CT scan is frequently obtained with the images taken immediately following injection of contrast. This test is beneficial in determining renal perfusion and the presence of major renal fractures, but it is unable to accurately determine the presence of urinary extravasation and will miss the majority of isolated ureteral injuries.[2,19,20] In the unstable patient requiring emergent laparotomy with no preoperative imaging studies, once the patient is stabilized in the operating room, a one-shot intravenous pyelogram (IVP) (2 mL/kg intravenous bolus of contrast) with the x-ray taken 10–15 minutes following injection of contrast may be beneficial in determining a normally functioning contralateral kidney if unilateral nephrectomy is a consideration.[21] As an alternative to the single-shot IVP, a CT can be delayed until after the patient is resuscitated and stabilized; if necessary, definitive surgical repair of GU injury can often be deferred for 12–24 hours, as long as the patient's condition permits it.[4,22]

Indications and Use of Arteriography

As many as 25% of grade 3 and 4 renal trauma managed by nonoperative protocols will require angiography and selective angioinfarction of bleeding vessels for persistent or delayed renal hemorrhage.[23,24] Clinical signs of persistent bleeding are hematuria associated with blood clots in the voided or catheterized bladder and a falling serial hemoglobin. Orthostatic blood pressure alterations are a late finding in the pediatric population.[4,23,25–27] Delayed hemorrhage classically develops 10–14 days postinjury, but may occur up to 1 month later. Delayed hemorrhage usually arises from the development of arteriovenous (AV) or pseudoaneurysm malformations.[4,25–27] Unlike AV malformations arising from a renal biopsy, AV malformations following renal fractures rarely, if ever, resolve spontaneously. Nearly all require active intervention.[4,25–27]

Superselective angiographic embolization of isolated renal artery branches for persistent or delayed hemorrhage has a success rate approaching 80%. This is the preferred treatment method for persistent or delayed bleeding, with surgical exploration reserved for angioembolization failure.[4,25–28] Occasionally, angiographic embolization is used to treat persistent urinary fistulas. In this clinical scenario, a functionally transected renal fragment following a high-grade renal injury is completely separated from the renal collecting system, and a persistent urinary fistula develops despite management by a double-J stent and/or a percutaneous nephrostomy tube. In these unusual patients, selective angiographic embolization can be performed to resolve the urinary fistula by necrosing the isolated functional renal fragment.[4,29]

Postembolization syndrome (fever, flank pain, and an adynamic ileus) is a well-recognized and self-limiting condition that occurs after angiographic embolization. Symptoms usually resolve by the fifth postembolization day.[4,30–33] Bacterial seeding of either the necrotic renal tissue or the hematoma from the angiographic intervention must be ruled out in patients with postembolization fever. It is therefore mandatory to obtain blood and urine cultures if a febrile response develops postembolization. In this setting, the clinician should consider a repeat CT scan with possible aspiration and culture of the hematoma or urinoma if symptoms persist for 5 or more days after embolization.[4,33]

Indications and Use of Retrograde Pyelography and Percutaneous Drainage

In patients with a history of trauma, two indications exist for performing retrograde pyelography. First, it can be

TABLE 34.1 Grading of renal injuries

Grade of renal injury	Description
1	Renal contusion or subcapsular hematoma
2	Nonexpanding perirenal hematoma, <1 cm parenchymal laceration, no urinary extravasation, all renal fragments viable
3	Nonexpanding perirenal hematoma, >1 cm parenchymal laceration, no urinary extravasation, renal fragments may be viable or devitalized
4	Laceration extending into the collecting system with urinary extravasation—renal fragments may be viable or devitalized, or injury to the main renal vasculature with contained hemorrhage
5	Completely shattered kidney—by definition multiple major lacerations of >1 cm associated with multiple devitalized fragments, or injury to the main renal vasculature with uncontrolled hemorrhage, renal hilar avulsion

used to rule out the presence of a partial or total ureteral disruption; second, it can aid in the placement of a double-J ureteral stent for the management of a symptomatic urinoma.[2–6,19,28,34–36] Most posttraumatic urinomas are symptomatic. Approximately three-fourths of urinomas resolve spontaneously.[4,34,37–39] *Persistence of the urine collection may be associated with persistent flank pain, adynamic ileus, and/or low-grade temperature, necessitating either percutaneous or endoscopic intervention.*[34] Cannon and colleagues determined that conservative management is more likely to fail in patients with no contrast in the ipsilateral ureter, those with a large separation of the upper and lower poles, children with multiple areas of extravasation, and patients with blood transfusion requirements.[40] Although percutaneous drainage and internal stenting are both efficacious, the major advantages to internal drainage include improvements in quality of life during convalescence, specifically avoidance of external catheter care, and the reduced risk of inadvertent tube dislodgment.[4,34,37,41] A disadvantage of internal drainage is that stent placement and removal requires general anesthesia in the child. In addition, smaller ureteral stents (4–5 French) placed in young children can become blocked with debris and blood clots from the dissolving hematoma. Percutaneous nephrostomy tubes should be considered in the following three scenarios: (1) after failure of endoscopic intervention, (2) when managing unstable patients who may not tolerate general anesthesia, and (3) when managing patients at risk for stent obstruction due to debris or hematoma.[34,37]

Indications and Use of DMSA and Follow-Up Radiographic Imaging Following Renal Trauma

Follow-up imaging is typically unnecessary for grade 1 and 2 renal injuries, unless the clinical scenario suggests progressive pathology, as indicated by unrelenting hypertension, fever, dropping hemoglobin, hemodynamic instability, worsening flank pain, progressing renal failure, or persistent hematuria. In patients with grade 3, 4, or 5 renal injuries, we recommend that a repeat CT scan with delayed images be obtained 2–3 days after the traumatic insult. This study assesses the extent of the hematoma or urinoma and functions as a baseline evaluation in case delayed hemorrhage occurs.[4,6] Additional repeat CT scans may be considered depending on the clinical scenario.[6] We also recommend that a 3-month follow-up CT scan be performed in all grade 3–5 renal injuries. This latter study is used to verify resolution of a perinephric hematoma or urinoma and to define the anatomic configuration of the residual functioning renal parenchyma.[9] The nature of follow-up imaging, though, is controversial; other authors have reported successful outcomes using only ultrasonography on children following blunt renal trauma after initial staging, reserving CT scanning for selected patients with clinical symptoms or sonographic findings suggestive of progressive pathology.[42]

Nuclear renal scanning using dimercaptosuccinic acid (DMSA) allows the physician to determine renal cortical function and differential renal function. Serial DMSA scans have revealed that little, if any, renal parenchyma recovers function after 7 days postinjury; therefore, a DMSA scan obtained more than 1 week after the injury provides a valid estimate of subsequent renal function.[43,44] We suggest that all patients with grade 3 injuries with devitalized fragments, all patients with grade 4 and 5 injuries, and all patients with persistent posttraumatic hypertension be evaluated with a quantitative radionuclide scintography, preferably DMSA, at least 1 week following the trauma.[4,43] Provided the serum creatinine is normal, a differential renal function exceeding 30% suggests satisfactory function that would prevent renal failure in the event that the uninjured kidney is lost.[4,39,44]

EFFECT OF ETIOLOGY ON THE MANAGEMENT OF TRAUMATIC GU INJURIES

Blunt versus Penetrating Genitourinary Trauma

The etiology of the traumatic injury plays an important role in determining the management of the patient. In North America, blunt trauma, usually due to high-velocity or deceleration injury, causes 90% of renal injuries in children. Fewer than 2% of children with blunt trauma require radiographic or surgical intervention.[4,6,9,38] Approximately 10% of traumatic pediatric renal injuries are due to penetrating trauma. In the presence of penetrating trauma, the physician should immediately triage the patient into one of two groups depending on the source of the penetrating trauma: either a stab or low-velocity penetrating wound group or a high-velocity penetrating wound group.[4,6,9] Although penetrating trauma results in the risk of wound contamination by outside material, several studies have shown that a selective nonoperative approach to the management of patients with a stab wound and, in very select cases, low-velocity gunshot wounds can be safely implemented.[4,25,45,46] *In hemodynamically stable patients with a penetrating wound posterior to the anterior axillary line, intravenous antibiotics are initiated and a screening triphasic abdominal and pelvic CT is obtained.* In these patients, surgical exploration or laparoscopy is indicated for persistent blood loss, the presence of air in the peritoneum, signs of developing peritonitis, or radiographic findings consistent with a ureteral injury.[4,25,46–49]

Gunshot wounds to the trunk are associated with a GU injury approximately 15% of the time.[47] In patients with GU trauma secondary to a gunshot wound, the kidney is the site of injury in approximately 60% of the patients, the bladder in 20%, the urethra in 5%, and the ureter in 2%; 13% will have two or more GU injuries.[47,50] If a GU structure is traumatically damaged due to a gunshot wound, the likelihood of associated organ injury is approximately 90%.[23,47,50] While the majority of blunt renal trauma and the majority of penetrating renal trauma from stab wounds are amenable to complete radiographic staging and nonoperative management, gunshot wounds to the abdomen often result in a hemodynamically unstable patient with multiple associated organ injuries requiring urgent

TABLE 34.2 Consensus recommendations for management of renal trauma

Clinical findings and/or grade of renal injury	Recommended treatment
Grade 1 or 2 renal injury irrespective of traumatic etiology[a]	Nonoperative
Isolated grade 3 or 4 and hemodynamically stable grade 5 renal injuries	Nonoperative
Uncontrollable renal hemorrhage/vascular instability (usually grade 4 vascular or the vast majority of grade 5 injuries)	Absolute requirement for surgical intervention
Persistent or delayed hemorrhage not responding to angiographic embolization	Absolute requirement for surgical intervention
Expanding pulsatile retroperitoneal mass found on surgical exploration for coexisting intra-abdominal injuries	Absolute requirement for surgical intervention (verify contralateral renal function prior to exploration)
Penetrating trauma, inadequate preoperative radiographic staging due to vascular instability of patient, retroperitoneal hemorrhage found on exploration	Retroperitoneal (renal) exploration strongly recommended (verify contralateral renal function)
Blunt trauma; inadequate preoperative radiographic staging due to vascular instability of patient; coexisting intra-abdominal injuries, especially stomach, duodenum, pancreas, and colon; retroperitoneal hemorrhage found on exploration	Retroperitoneal (renal) exploration recommended (verify contralateral renal function)
Blunt trauma; radiographic screening studies reveal grade 3, 4, or 5 renal injury; coexisting intra-abdominal injuries, especially stomach, duodenum, pancreas, and colon	Retroperitoneal (renal) exploration recommended

[a] Assuming adequate radiographic staging and no absolute indication for exploration.

laparotomy.[45] The need for emergent surgery excludes the ability to adequately stage the renal injury.[23,24,47] If the patients with a gunshot wound can undergo adequate radiographic staging, isolated grade 1 or 2 renal injuries can be managed successfully with a nonoperative approach with minimal complications (Table 34.2).[44]

Gunshot wounds caused by high-velocity missiles (>350 m/s) deserve special consideration. The kinetic energy of a high-velocity bullet creates a surrounding energy wave 30–40 times the missile diameter. In addition, the missile will frequently yaw or tumble during penetration. The combination of blast injury and missile tumbling results in extensive damage to the surrounding tissues at a large distance from its path.[6] With high-velocity gunshot wounds to the torso, radiographic and/or surgical evaluation at the time of the assault may not reveal the presence of a GU injury. In some patients with a high-velocity injury, the renal pelvis and/or ureter will appear intact or perhaps only slightly contused at the time of the radiographic examination and/or surgical exploration. As the high-velocity blast injury matures, necrosis of the ureter or portions of the renal pelvis may develop. The extent of the GU injury often comes to attention days later, as urinary extravasation develops due to delayed necrosis.[4,51,52]

MANAGEMENT OF RENAL TRAUMA

Multiple studies have stated that the nephrectomy rate in patients with traumatic renal injuries is higher with surgical exploration than with nonoperative management.[39,46,53–56] These reports suggest that hemorrhage from the severely injured kidney is tamponaded by the intact Gerota's fascia. Surgical exploration in these cases disrupts the fascia, resulting in uncontrollable renal bleeding and the need for emergent nephrectomy. This reasoning is controversial. With the enhanced ability of the CT scan, we are now more accurately staging renal injuries. With the development and application of trauma-related severity scores, the need for emergent nephrectomy during renal exploration has seemed to be related more to the severity of the initial renal injury, and multiple coexisting injuries and related intraoperative hemodynamic instability, rather than to disruption of Gerota's fascia. Nephrectomy in this situation is performed for expediency to save the hypothermic, coagulopathic, and clinically unstable patient.[4,37,57–60]

Due to this controversy, three different concepts have been suggested to best determine the management of coexisting intra-abdominal trauma and grade 3 or higher renal injuries:

1. Observation unless an absolute indication for renal exploration exists, regardless of the mechanism of injury.[39,46,51]
2. Renal exploration and renorrhaphy of a grade 3 or higher renal injury. This should be completed if a laparotomy is to be performed for a coexisting intra-abdominal injury. If renal exploration is performed, we recommend that control of the renal vessels medial to Gerota's fascia be obtained before renal exploration.[4,6,37,61] In this setting, control of the renal vessels prior to opening Gerota's fascia may prevent life-threatening hemorrhage. With passage of time, even the need for vascular control before renal exploration has become controversial, with some studies revealing the incidence of nephrectomy being equivalent whether or not prior vascular control is used.[4,6,58,61]
3. Exclusion of renal exploration in patients with concurrent intra-abdominal injuries, provided the trauma surgeon separates the enteric injury from the urinary tract injury with omentum or other alternative tissue and places perioperative drains. It is hypothesized that the separation of the enteric or pancreatic injury from the GU injury, along with the placement of perioperative drains, will prevent breakdown of enteric repairs

by leaking urine and/or help prevent the development of urinary tract complications by removal of excess contaminating bacteria or pancreatic enzymes away from the site of the GU injury.[6,37,57,62,63]

The current recommendations for operative intervention are based on three findings: the hemodynamic stability of the patient, an accurate radiographic staging of the renal trauma, and the presence of associated organ injury.[4,6,23,34,37] Absolute indications for renal exploration include life-threatening hemorrhage from a renal source (usually grade 4 vascular and the majority of grade 5 renal injuries), a pulsatile expanding retroperitoneal hematoma found during emergent laparotomy, and persistent or delayed renal bleeding refractory to angioinfarction.[4,6] It is also strongly recommended that patients with penetrating trauma found to have a retroperitoneal hematoma in the absence of adequate preoperative imaging be explored once contralateral renal function is verified by an intraoperative single-shot IVP.[4,6]

The ideal candidate for nonoperative management is the hemodynamically stable patient sustaining either blunt or penetrating trauma and grade 1 or 2 renal injury, with or without associated intra-abdominal injuries. GU complications in this subset of patients are minimal.[4,6,23] In patients with isolated grade 3 or 4 renal injuries, angiographic, endoscopic, or percutaneous intervention is required in up to 55% of them. Intervention is necessary for delayed bleeding in approximately 25%, and for symptomatic urinomas in approximately 25%. Surgical exploration to control complications not amenable to nonoperative techniques will develop in approximately 5%. In essence, conservative management of isolated grade 3 or 4 renal injuries will avoid approximately 95% of open surgical intervention.[4,6,9,23,34,37,62,64]

Contemporary series are plagued with small cohorts of children with higher-grade injuries; however, when pooling data together, it is evident that conservative approaches toward blunt renal trauma have resulted in high renal preservation rates.[28,35,36,45,64–72] Table 34.3 lists contemporary series of children with blunt grade 4 and 5 renal injuries managed conservatively. Of the 144 children with grade 4 trauma, there is a 96% renal preservation

TABLE 34.3 Outcomes of conservative management in contemporary high-grade renal trauma series

Author	*n*	Nephrectomy	Open repair	Endoscopic/percutaneous management
Grade 4				
Fitzgerald et al.[72]	6	0 (0%)	1 (17%)	0 (0%)
Mohamed et al.[65]	14	0 (0%)	5 (36%)	5 (36%)
Henderson et al.[66]	35	1 (3%)	3 (9%)	1 (3%)
Broghammer et al.[67]	10	1 (10%)	1 (10%)	0 (0%)
Buckley and McAninch[9]	11	0 (0%)	4 (38%)	0 (0%)
El-Sherbiny et al.[64]	4	0 (0%)	0 (0%)	2 (50%)
Nance et al.[35]	11	1 (9%)	0 (0%)	5 (45%)
Rogers et al.[36]	10	0 (0%)	1 (10%)	2 (20%)
Margenthaler et al.[68]	14	3 (21%)	1 (7%)	0 (0%)
Nguyen and Das[69]	9	0 (0%)	0 (0%)	0 (0%)
Russell et al.[70]	15	0 (0%)	1 (7%)	5 (33%)
Wessel et al.[71]	5	0 (0%)	5 (100%)	0 (0%)
Total	**144**	**6 (4%)**	**22 (15%)**	**20 (14%)**
Grade 5				
Fitzgerald et al.[72]	1	0 (0%)	0 (0%)	0 (0%)
Eassa et al.[28]	18	4 (22%)	2 (11%)	5 (28%)
Mohamed et al.[65]	10	2 (20%)	7 (70%)	0 (0%)
Henderson et al.[66]	15	3 (20%)	1 (7%)	0 (0%)
Broghammer et al.[67]	2	1 (50%)	0 (0%)	0 (0%)
El-Sherbiny et al.[64]	3	0 (0%)	0 (0%)	2 (67%)
Nance et al.[35]	2	0 (0%)	0 (0%)	1 (50%)
Rogers et al.[36]	10	7 (70%)	6 (60%)	0 (0%)
Margenthaler et al.[68]	5	3 (60%)	0 (0%)	0 (0%)
Nguyen and Das[69]	5	5 (100%)	0 (0%)	0 (0%)
Wessel et al.[71]	1	1 (100%)	0 (0%)	0 (0%)
Total	**72**	**26 (36%)**	**16 (22%)**	**8 (11%)**

rate. Fifteen percent underwent open surgery, consisting of partial nephrectomy, renorrhaphy, or pyeloplasty, and 14% were primarily managed with minimally invasive procedures, such as ureteral stenting, nephrostomy, or angioablation. Of the 72 children with grade 5 trauma, we tabulated a 64% renal preservation rate, with 22% of patients requiring an open repair and 11% needing endoscopic or percutaneous intervention. These renal preservation rates, though, are likely overestimates, as Keller et al. reported significant renal scarring volume loss in the majority of children following conservative management of grade 4 and 5 trauma.[39]

The recommendations for treating a patient with a history of blunt abdominal trauma who has either inadequate radiographic staging and a nonexpanding and nonpulsatile retroperitoneal hematoma found on surgical exploration, or a known grade 3 or higher renal injury undergoing laparotomy for associated intra-abdominal trauma are more controversial. In these situations, the urologist should be aware of the relationship between the associated organ injury and the severity of the renal injury, and how these two factors relate to GU morbidity. For example, if a colonic injury and a retroperitoneal hematoma are simultaneously present, approximately 10% of patients will be found to have a grade 1 or 2 renal injury, and 90% will have a grade 3 or higher renal injury.[4,6,23] In addition, if a colonic or pancreatic injury is concurrently present with devitalized renal tissue, nonoperative management of the renal injury is associated with a three- to fourfold higher incidence of complications compared with renal exploration and renorrhaphy. In addition, renal exploration in these latter patients does not appear to result in increased risk of nephrectomy.[9,37,57,59] Knowledge of these facts has resulted in the consensus that *patients with a known grade 3 or higher renal injury undergoing exploratory laparotomy for multiorgan injury induced by blunt trauma should undergo renal exploration with renorrhaphy and the placement of retroperitoneal drains*. It is also accepted that patients undergoing emergent laparotomy without adequate preoperative radiographic studies who are found to have colonic or pancreatic injuries and a coexisting retroperitoneal hematoma should have a single-shot IVP obtained to verify contralateral renal function and proceed with renal exploration (Table 34.2).[4,6,9]

Nonoperative Therapy for Renal Trauma

Nonoperative therapy consists of bed rest, close monitoring of the vital signs and urine output, serial abdominal examinations, serial hemoglobin and hematocrit determinations, and transfusion as indicated. In the patient with a grade 3 or higher renal injury, massive blood loss and vascular instability may rapidly appear. The patient managed in this fashion should have blood immediately available. Repeat CT imaging of the kidney 2–3 days following trauma is recommended in patients with grade 3–5 renal injuries. CT imaging should be obtained earlier if prompted by clinical indications (see the "Indications and Use of DMSA and Follow-Up Radiographic Imaging Following Renal Trauma" section). If the child remains hemodynamically stable with or without transfusions and CT verifies a stable or resolving urinoma and/or hematoma, observation can continue. If the child becomes hemodynamically unstable or continues to have a falling hemoglobin or hematocrit despite transfusions, renal angiography with selective angioinfarction of the bleeding site should be attempted prior to formal surgical repair. If the patient with a urinoma complains of chronic or increasing flank pain, or has a persistent low-grade fever and/or a persistent ileus, consideration for endoscopic or percutaneous management of the urinoma is required. The patient may be allowed to walk as soon as gross hematuria has resolved. Resumption of strenuous physical activity is prohibited for 6 weeks.[4,6,9,23,24]

Due to the risk of wound contamination, we recommend intravenous broad-spectrum antibiotics in patients with a renal injury secondary to penetrating trauma on a nonoperative protocol. In renal injuries following blunt trauma, antibiotics may be considered if a large retroperitoneal hematoma or urinary extravasation is present. In this latter situation, the presence of an indwelling urethral catheter and/or multiple intravascular catheters may cause bacterial colonization of the urine or blood and may hypothetically result in an infected hematoma or urinoma.[4,6,9,23,24]

Operative Intervention for Renal Trauma

Renal salvage by renorrhaphy or partial nephrectomy requires complete exposure of the injured kidney, debridement of nonviable tissue, suture ligation of bleeding arterial vessels, and repair of collecting system injury. Defects in the renal parenchyma may be closed primarily with renal capsule. For larger defects, we prefer the placement of small pieces of Gelfoam wrapped in Surgicel directly into the parenchymal defect and closure of the renal capsule defect with woven polyglycolic acid mesh. Alternatively, perinephric fat, omentum, or thrombin-soaked Gelfoam may be used to pack the parenchymal defect. A watertight closure of the collecting system is not always possible and may be inadvisable. If the renal pelvis or ureter is closed with tension, tissue ischemia and delayed resolution of urinary leakage may occur. If a major violation of the urinary drainage system is present, placement of intraoperative ureteral stents and/or a nephrostomy tube should be considered. Adequate drainage of the perinephric area following repair is vital. In the presence of concurrent stomach, duodenal, pancreatic, and colonic injuries, interposition of omentum or peritoneum between the site of the major renal injury and the site of the coexisting intra-abdominal injury is usually necessary. Nephrectomy should be considered in irreparable grade 4 or 5 renal injuries and in hemodynamically unstable patients with multiorgan trauma.[4,6]

RENAL VASCULAR INJURIES

The kidney is an end organ; only rarely is collateral blood flow sufficient to maintain renal function if a segmental or main renal artery is damaged. In a patient sustaining renal arterial trauma, the clinical triad of decreased or absent renal arterial blood flow, inadequate collateral blood flow, and warm ischemia time almost invariably results in the loss of renal function.[4,6] *Therefore, no attempt to repair injuries to segmental renal vessels should be considered,*

and repair of the traumatically injured main renal artery is rarely indicated.[36] In essence, reconstruction of the main renal artery following trauma should only be considered in patients that are hemodynamically stable with an injury to a solitary kidney or in patients with bilateral renal injuries; otherwise, nephrectomy is the most expeditious and least moribund treatment. The infrequent exception to this rule is the presence of an incomplete renal arterial injury where perfusion to the kidney has been maintained by flow of blood either through the partially occluded main renal artery or via collateral vessels.[4,6]

Renal artery thrombosis is rare, occurring in as low as 0.1% of patients presenting with blunt abdominal trauma.[73] The injury is typically associated with acceleration–deceleration injuries, resulting in subintimal dissection and vascular thrombosis. Vascular compression by the vertebrae can also propagate intimal trauma, resulting in thrombosis. Hemodynamically stable patients without concomitant injuries necessitating exploration may be managed with arteriography and endovascular stenting.[74] Successful revascularization is dependent on ischemia time, with success rates dropping off dramatically after 2–3 hours; however, durable recovery of kidney function has been demonstrated following endoscopic revascularization after up to 1 week of ischemia following traumatic renal artery occlusion.[75] Endovascular stenting has also been utilized successfully in the management of penetrating renal artery trauma in children.[76] Unfortunately, the evidence for endovascular stenting as management for renal artery thrombosis or hemorrhage in children is limited to small series and case reports.

TRAUMATIC-INDUCED RENAL VASCULAR HYPERTENSION

The most common causes of posttraumatic renal hypertention are renal ischemia from segmental artery occlusion, main renal artery occlusion with intact peripheral blood flow to the kidney, a traumatically induced AV malformation, and compression of the renal parenchyma by hematoma or fibrosis (the Page kidney model). The presence of hypertension immediately following the traumatic insult may be secondary to pain; however, persistent hypertension 30 days postinjury could be due to a renal source, and the diagnosis of traumatically induced renovascular hypertension should be considered. The incidence of traumatically induced hypertension after renal injury is reported to be around 6% in contemporary grade 4 or 5 pediatric renal trauma series.[28,35,64–67,70,72]

Hypertension from renovascular trauma will usually develop within 36 months of injury.[4,6] If sustained hypertension develops, evaluation with a DMSA scan to determine differential renal function and radiographic studies (MRI or CT angiography) should be performed to rule out the development of an AV fistula. Hypertension related to an AV malformation should initially be treated with angiographic embolization. If consideration for surgical intervention is entertained, renal vein renin sampling for split renin ratios should be considered. The latter is especially helpful in the presence of segmental renal scarring where partial nephrectomy is a consideration for surgical management. The most common clinical finding in posttraumatic-induced hypertension; however, a small poorly functioning kidney (<30% differential renal function) is also associated with scarring. Most authorities believe that a differential renal function of <30% would not prevent the onset of renal failure in the event that the uninjured kidney is lost.[4,6,39,44] Nephrectomy or partial nephrectomy is therefore the treatment of choice for posttraumatic hypertension.[28] Rarely is renal revascularization of any benefit since hypertension is almost invariably produced by the production of increased renin from intrarenal or subcapsular fibrosis. Surgical treatment of hypertension by decortication of subcapsular fibrosis in patients with a Page kidney–induced hypertension has been published; however, the long-term results of this surgical treatment modality are extremely controversial.[4,6]

URETEROPELVIC JUNCTION DISRUPTION

If the screening CT evaluation reveals the presence of medial and perirenal contrast extravasation with no visualization of the ipsilateral distal ureter on delayed images, the diagnosis of either a large laceration of the renal pelvis or an avulsion of the UPJ is entertained and mandates further investigation with either a retrograde pyelogram or surgical exploration.[4,6,19] *Disruption of the UPJ is most commonly caused by acceleration–deceleration injuries (fall from >15 feet) or by sudden extreme hyperextension of the trunk (pedestrian–vehicle collision or patient thrown from the vehicle during a motor vehicle accident).* The mechanism of injury is due to a sudden displacement of the more mobile kidney associated with a relatively fixed ureter, with force vectors from the traumatic impact interacting at the UPJ.[2,3,19]

Although some may suggest that a large extrarenal pelvis or a congenital UPJ obstruction renders the patient more susceptible to disruption of the UPJ, this is controversial. The vast majority of patients with a congenital UPJ or congenital hydronephrosis with a traumatic injury will be found to have a rupture of the renal pelvis or a major laceration through a thinned renal cortex, not a UPJ disruption.[2,3,5,19] Generally, a laceration of an enlarged renal pelvis will appear as an isolated renal injury, whereas a UPJ disruption tends to occur in association with life-threatening injuries. The majority of patients sustaining a UPJ disruption will present with vascular instability, requiring emergent laparotomy, with the patient unable to undergo preoperative imaging. *Up to 30% of patients with a UPJ disruption will have a completely normal urinalysis, without any degree of hematuria.* In the patients undergoing exploratory laparotomy for coexisting intra-abdominal injury, exploration rarely reveals a retroperitoneal hematoma. Due to the frequent association of this injury with life-threatening trauma, inadequate preoperative radiographic staging studies, and the absence of a retroperitoneal hematoma, the diagnosis of a UPJ disruption is delayed for >36 hours in more than 50% of patients. Patients will eventually come to attention due to persistent postoperative fever, flank pain, ileus, or sepsis.[2,3,19,20,36,66,67]

Three classic findings on a triphasic CT scan are associated with UPJ disruption: (1) good renal contrast excretion with extravasation around the upper ureter into the medial perirenal space, (2) absence of parenchymal lacerations and intact renal calices, and (3) nonvisualization of the ipsilateral ureter. When a diagnosis of a possible disruption of the UPJ is entertained, careful evaluation of the delayed CT images is necessary. This diagnosis may be difficult even if suspected. Specifically, the severely injured patient usually has a history of volume depletion; contrast excretion due to the coexistence of hypovolemia, acute tubular necrosis, or renal contusion may be minimal. To definitively rule out the presence of a UPJ disruption, it is necessary to confirm the presence of contrast material in both distal ureters. This can be especially difficult in patients where this injury may be associated with a grade 3 renal injury, where contrast material may be preferentially accumulating in the retroperitoneum. If the results of the CT scan remain inconclusive, a retrograde pyelogram should be performed.[2–4,6,19,20]

In children with preexisting hydronephrosis from a UPJ obstruction, the site of injury is frequently a major laceration through a thinned renal cortex (grade 3 renal injury) or a laceration of the renal pelvis, not disruption of the UPJ. These patients should have a retrograde pyelogram to confirm continuity of the UPJ, and if not suspicious for disruption, it can then be safely managed with either a percutaneous nephrostomy or double-J stent placement with delayed pyeloplasty performed after stabilization of the patient.[3,5,34,36,63,72]

In patients with UPJ disruption, the delay in diagnosis may last up to 3 months following the injury and may significantly increase the risk of nephrectomy.[5,19,20] In the clinically stable patient where the diagnosis is made within 5 days of the trauma, we prefer to proceed to surgical repair with debridement of any devitalized ureteral tissue, spatulation, and reanastomosis of the ureter over a stent, with concurrent placement of an intraoperative nephrostomy tube and retroperitoneal drain. Since the area of ureteral necrosis may extend for 2–3 cm, mobilization and downward displacement of the kidney may be necessary to obtain a tension-free ureteral anastomosis.[19,20] In patients with a delayed diagnosis of a UPJ disruption 6 or more days posttrauma, we prefer to place a nephrostomy tube and allow the injury to stabilize over 6–8 weeks. Differential renal function is then obtained via DMSA scan and the length of the ureteral injury ascertained by a combined anterograde and retrograde pyelogram. The combination of percent renal function and the length of the ureteral defect will allow the surgeon to make the proper surgical planning. Surgical alternatives in this situation include a primary ureteroureterostomy, an ileal ureter, autotransplantation, and nephrectomy (indicated if the split renal function is <30% in the presence of a normal serum creatinine and renal clearance).[4,6,19,20,36]

ACTIVITY LIMITATIONS IN CHILDREN WITH SOLITARY KIDNEYS

Children with solitary kidneys warrant special attention. The American Academy of Pediatrics revised their activity recommendations for children in 2001, recommending no restrictions for noncontact sports, and conditional participation in contact activities. The recommendations stop short of fully endorsing full-contact sports, but advise informed caution and individual assessment of the potential risks associated with exposing a solitary kidney to potential trauma.[77] To evaluate this further, we tabulated the causes of high-grade renal trauma, as reported by contemporary renal trauma series published over the past 12 years.[28,36,64,65,67,70,72,78] Of the 146 reported cases of grade 4 or 5 renal trauma, causes included motor vehicle accidents (42%), falls (37%), pedestrian–vehicle collisions (10%), blunt torso trauma (4%), bicycle accidents (4%), contact sports (3%), sled accidents (2%), abuse (1%), skateboards (1%), and all-terrain vehicle accidents (1%). Given that the overall nephrectomy rate in grade 4 or 5 renal trauma patients in these series was 12%, the risk of being rendered anephric by participation in contact sports is exceedingly low. It would stand to reason that children with solitary kidneys participating in contact sports would be more likely to lose their remaining kidney from the car ride to football practice than by the practice itself.

Johnson et al. evaluated 6 years of data from the National Pediatric Trauma Registry.[79] Of 813 renal injuries, renal loss occurred in 28 children, 75% of which were due to motor vehicle accidents, falls, and pedestrian–vehicle collisions. A total of seven nephrectomies were performed; they were associated with sledding, skiing, rollerblading, jet skiing, and horseback riding. No high-grade renal injuries or renal losses were due to contact sports.

We recommend that patients with solitary kidneys be counseled on the risk of high-grade renal trauma with high-speed recreational activities, and be encouraged to wear safety belts, when possible. Participation in contact sports should not be discouraged due to the presence of a solitary kidney.

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Section 4

The Ureter

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CHAPTER 35

The Ureter

Martin Kaefer

GENERAL

The goal of this chapter is to provide an overview of the embryology, general physiology, and molecular mechanisms responsible for normal ureteral development and function. The pathophysiology of the most common pathological abnormalities to afflict the ureter are thereafter described. Processes that affect the ureter are ultimately important because of their impact on kidney physiology. The reader is directed to chapters that specifically focus on alterations in renal function secondary to infection, ureteral obstruction, and vesicoureteral reflux (VUR) for more details on this subject.

EMBRYOLOGY AND ANATOMY

During the fourth week of gestation, the development of the ureter begins as an outpouching of the mesonephric duct, termed the ureteric bud (Figure 35.1). The development of this structure is heavily influenced by molecular factors released from the mesodermal tissue mass, which is destined to become the renal parenchyma (i.e., the metanephric blastema). At 28 days, the ureter consists of an epithelial tube surrounded by loose mesenchymal cells. Transient luminal obstruction ensues with subsequent recanalization during the seventh week of gestation.[1,2] It appears that this recanalization process begins in the midureter and extends in a bidirectional manner both cranially and caudally. It has been suggested that angiotensin, exerting its affect through the angiotensin II receptor (AT_2), may play a role in this recanalization process.[3] Chwalle's membrane, a two-layered cell structure, transiently divides the early ureteric bud from the urogenital sinus.[4] Subsequent dissolution of this membrane results in unimpeded flow of urine from the kidney into the bladder.

The first signs of ureteral muscularization are seen at 12 weeks of gestation. Smooth muscle differentiation is first noted at the ureterovesical junction (UVJ) and then ascends cranially toward the upper collecting system.[5] With time, these fibers, which are initially randomly arranged in the wall of the ureter, become more numerous and assume a more specific orientation.[6] The epithelium attains a transitional configuration by 14 weeks. Once fully developed, the muscular wall of the ureter is characterized as having an inner longitudinal, middle circular, and outer longitudinal layer. As the ureter penetrates the bladder, its muscular layers disperse. The outer layer melds into the detrusor in the upper part of the hiatus to form Waldeyer's sheath, which attaches the ureter to the bladder and is in continuity with the deep trigone.[7] As the ureter makes its transition to an intramural location, the muscle fibers take on a primarily longitudinal orientation.[8] The longitudinal muscle fibers spread out to form the borders of the superficial trigone.

Proper development and spatial orientation of the ureter as it combines with the bladder are dependent on a number of molecular factors. The renin–angiotensin system appears to play a major role in ureteral development. AT_2 is expressed in high concentration by the mesenchymal cells that are positioned adjacent to the ureteric bud at early developmental stages. The fact that expression of this receptor markedly decreases after birth supports the contention that AT_2 might play an important role in ureteral development.[9] Mice in whom the AT_2 gene has been knocked out demonstrate a high incidence of congenital anomalies of the urinary tract, including VUR, UVJ obstruction, and megaureter.[10] These structural anomalies may result from delayed apoptosis of the mesenchymal cells surrounding the ureteric bud. The clinical relevance of these experimental findings has been underscored by the identification of a select group of patients with mutations at this locus who possess a syndrome that includes ureteropelvic junction obstruction and megaureter.[11]

Proper spatial orientation of the ureter is likely dependent on genes responsible for cell specification and body segmentation. The PAX family of genes has been extensively studied in this regard.[12] These genes appear to play a role in the interplay between the ureter and the developing kidney.[13] PAX mutations have been implicated in syndromes with VUR and renal anomalies and are inherited in an autosomal dominant manner.[14] However, to date mutations neither in the PAX genes nor in other genes involving body segmentation have been demonstrated to any significant degree in patients with familial VUR.[15]

URETERAL PHYSIOLOGY

Function of the Ureter

The function of the ureter is to effectively transport urine from the renal pelvis to the bladder in a unidirectional

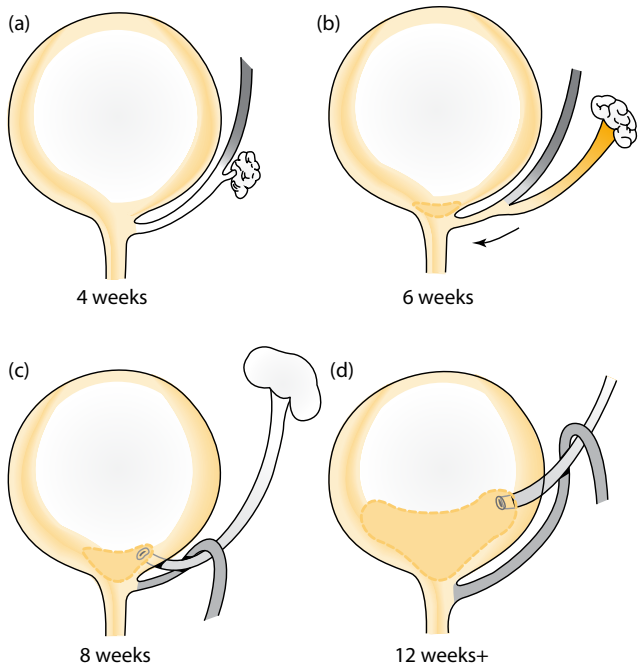

FIGURE 35.1 Embryology of ureter and trigone. The ureteral bud develops into the ureter and induces the metanephric blastema to differentiate and become the kidney. The common excretory duct (segment of mesonephric duct caudal to the ureteric bud) is absorbed into the bladder and becomes the deep trigone.

fashion. Coordinated antegrade movement of urine is initiated by pacemaker sites located in the renal pelvis and proximal ureter.[16–18] This electrical stimulus propagates caudally and, in so doing, gives rise to peristaltic activity of the ureteral musculature. Under healthy normal conditions, peristaltic contractions occur between two and six times per minute and advance down the ureters at a rate of between 2 and 6 mL/second.[19,20] The following section describes how events at the cellular level are translated into achieving this goal.

Electrical Excitation: Muscular Contraction

Unlike their skeletal muscle counterparts that receive a discrete stimulus from a motor end plate, smooth muscle cells of the ureter lack discrete neuromuscular junctions and depend on initiation of an action potential from pacemaker cells located in the renal pelvis and upper ureter. The ureter also receives neurologic input from numerous sources. Spontaneous electrical activity initiated by the pacemaker is in itself adequate to propagate electrical activity and induce coordinated peristaltic muscular activity. Evidence to support this contention includes the persistence of peristalsis after renal transplantation or denervation.[21,22] Individual muscle cells allow propagation of electrical activity through tight areas of cell-to-cell contact termed intermediate junctions.[23–25]

The parasympathetic and sympathetic nervous systems, as well as peptidergic substances (e.g., tachykinins, substance P, and neurokinin A) and nitric oxide, appear to have as their primary role the ability to modify ureteral contraction that has been initiated by the pacemaker unit.[26–28] Neuropeptides influence muscle activity via second messengers, including cAMP, cGMP, Ca^{2+}, inositol, 1,4,5-trisphosphate (IP_3), and diacylglycerol (DG). Upon binding of the specific effecter molecule to the cell receptor, the generation of these second messengers mediates the functional response through a process that frequently involves a cascade of protein phosphorylation. Release of these neurotransmitters is unlikely to exert the dominant force responsible for peristalsis. Physiologic support for this contention comes from the fact that treatment with specific neuropeptide antagonists (e.g., atropine in the case of the parasympathetic nervous system) often has little or no clinically significant effect on ureteral function.[29]

The smooth muscle cell is the structural element responsible for the effective mechanical transport of urine through the ureter. As in skeletal muscle, actin and myosin act as the two primary structural proteins that serve to provide active deformation of the cell during contraction and relaxation. Actin is bound to attachment plaques on the cell surface, which serve as an anchor point against which it can exert force on the cell membrane. Any process that results in a significant increase in Ca^{2+} in the region of the contractile proteins favors the development of a contraction. The phosphorylation of myosin is a key step in the contractile process. Phosphorylation of the myosin light chain allows actin to activate myosin Mg^{2+}-ATPase activity, leading to hydrolysis of ATP and the development of smooth muscle tension or shortening.

Function of the Ureterovesical Junction

The function of the ureterovesical junction is to facilitate the unidirectional, antegrade flow of urine from the ureter into the bladder. A number of passive and active factors play a role in maintaining this mechanism.

Facilitation of Antegrade Flow

After the urine bolus has progressed to the level of the UVJ, it is propelled into the bladder across the intramural ureteral segment. This process is facilitated by retraction of the ureter in a superolateral direction, in keeping with its primarily longitudinally oriented muscle. As a result, the resistance at the UVJ is lowered, facilitating antegrade fluid transport.[30]

Prevention of Retrograde Flow

Sampson was the first to propose a passive valvular mechanism created by the obliquity of the ureters as the ureter courses through the bladder wall, a mechanism that he named "ureteral lock."[31] Paquin demonstrated that in normal subjects (i.e., children without VUR), a 5:1 ratio of tunnel length to ureteral diameter existed.[32] In creating reflux by resecting the roof of the submucosal ureter in a pig model, Ransley and Risdon gave further support to the concept that ureteral tunnel length is of importance in maintaining a competent UVJ.[33]

In order for this passive mechanism to work successfully, the ureter must have an adequate muscle backing against which it can be compressed during bladder filling. In addition, the distal end of the ureter must be adequately anchored to the base of the bladder so that with filling, it

does not migrate laterally and experience a shortening of tunnel length. The importance of adequate muscle backing is supported by the increased incidence of VUR in patients with periureteral diverticuli. The passive mechanism for maintaining unidirectional urine flow across the UVJ is depicted in Figure 35.2.

The traditional concept of the ureterovesical antireflux mechanism consisted solely of this passive flap valve mechanism. However, a number of investigators have noted sufficient anatomic and physiological evidence to point to an active sphincteric mechanism.[34] The active valve function of the human ureter is thought to consist of a "vesicoureteral sphincter" that contracts in response to bladder contraction and relaxes after contraction of the external urethral sphincter.[35] Although an anatomically defined circumferential sphincter has not been identified, it has been postulated that a "physiological sphincter" exists.[36,37] During micturition, the longitudinal muscles of the UVJ are postulated to provide this "active" component by closing the meatus and submucosal tunnel. The alteration in ureteral jet pattern seen in patients with VUR has been cited by some investigators as evidence for this sphincteric mechanism.[38] Tanagho et al. demonstrated that prolonged electrical stimulation or administration of intravenous epinephrine can cause resistance to flow as contraction of the longitudinal muscle (which makes up part of the trigone) draws the orifice inferomedially.[8] The importance of trigonal attachment in maintaining an active valvular mechanism may vary from species to species. Hannan and Stephens, in excising the muscular component of the canine trigone, failed to demonstrate a significant increase in VUR in their model and concluded that the trigone did not play a major role in the function of the UVJ in this species.[39]

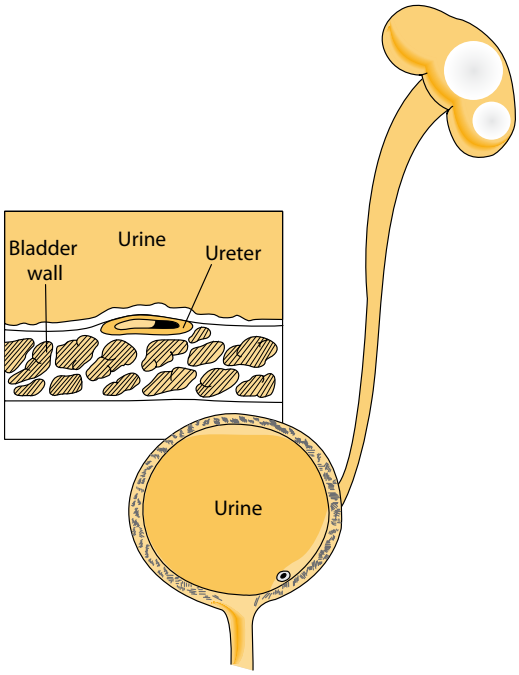

FIGURE 35.2 Flap valve mechanism: Urine compresses the ureter between the bladder mucosa and the bladder wall muscle, thus creating a flap valve mechanism that prevents reflux.

Synopsis of Urine Transport from Renal Pelvis to Bladder

A graphical representation of the process of urine transport from the renal pelvis to the bladder, as described by Griffiths and Notschaele, is shown in Figure 35.3.[40] The process begins when the production of urine results in a rise in the renal pelvic pressure. Urine is subsequently propelled into the upper ureter, which is initially in a collapsed state. A contraction wave originates in the most proximal portion of the ureter and moves the bolus of urine in front of it in a caudad direction. For efficient urine transport, the ureteral wall must completely coapt during the propagation of a urine bolus down the ureter.[41] The bolus that is pushed in front of the contraction wave lies almost entirely in a passive, noncontracting part of the ureter.[42] The resting pressure within the ureter, 0–5 cm H_2O, is similar to the intravesical pressure of the nondistended bladder. Peristaltic waves elevate this pressure to between 20 and 80 cm H_2O.[43] If the intraureteral pressure exceeds the intravesical pressure, urine will proceed into the bladder.

FACTORS INFLUENCING URETERAL FUNCTION

Many factors affect ureteral function. These typically are appreciated in the presence of either ureteral obstruction or VUR, both of which are described in the subsequent section. However, at times these factors may occur in the absence of these two major maladies. For example, ureteral dilatation may occur in the absence of obstruction

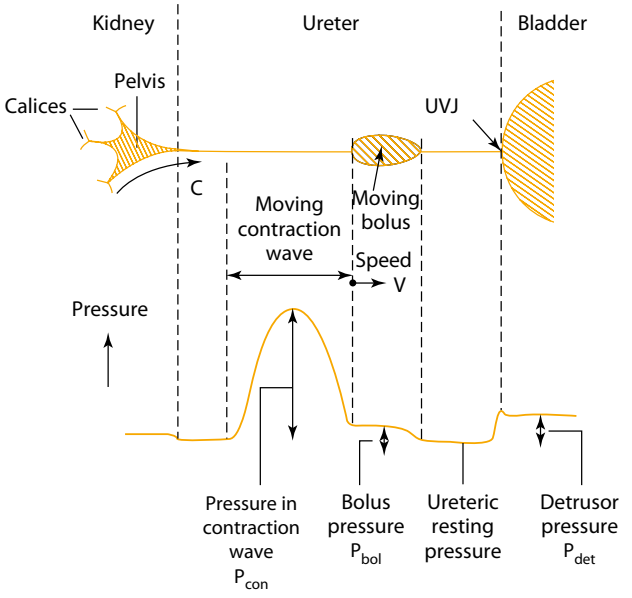

FIGURE 35.3 Schematic representation of a single bolus or urine in the ureter moving away from the renal pelvis and toward the bladder. Arrow C indicates the direction of bolus transport. The corresponding distribution of pressure within the urinary tract is shown in the lower tracing. (Adapted from Griffiths D, Notschaele C. *Neurourol Urodyn* 1983;2:155–6.)

or VUR in patients with high urine output secondary to diabetes insipidus.[44]

Ureteral Dilatation

Ureteral dilatation occurs due to either too much fluid entering or too little fluid exiting the ureter per unit time. Factors that influence the egress of urine from the ureter range from infection to high intravesical pressure to anatomic obstruction of the ureter. An increase in ureteral dimensions in and of itself adversely affects antegrade urine flow. As described by the Laplace equation, dilatation alters intraluminal pressure.

$$\text{Pressure} = \text{Tension} \times \text{Wall Thickness/Radius}$$

By increasing the luminal size (i.e., radius), the intraluminal pressure is diminished, decreasing the force propelling urine in a forward direction.[45]

Urine Volume

Hydration status and the ability of the kidney to concentrate urine affect the volume of urine transported per unit time through the ureters. Urinary concentrating ability is the first aspect of renal function to be affected in the presence of obstruction.[46] Evidence also exists that in the presence of VUR, the concentrating ability is altered.[47] With increasing urine flow rates, the initial response of the ureter is to increase peristaltic frequency. After the maximal frequency is achieved, further increases in urine transport occur by means of increases in bolus volume.[48,49] Eventually, the boluses coalesce and the ureter becomes filled with a continuous column of fluid.

Infection

Infection within the upper urinary tract may adversely affect urine transport. Experimentally induced pyelonephritis in a primate model has been associated with decreased peristaltic activity.[50] In vitro studies have shown that bacteria and *Escherichia coli* endotoxin can inhibit ureteral peristaltic activity.[51,52] Other investigators have not been able to suppress ureteral activity with endotoxin but have noted that growth media from *E. coli*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae* do inhibit ureteral contractility. These investigators suggested that the inhibition of peristaltic activity is due to an exotoxin.[53] In humans, irregular peristaltic contractions and alterations in the ureteral jet have been recorded with infection.[38,43] Ureteral dilatation has also been reported to result from retroperitoneal inflammatory processes, which presumably exert their effect via the transudation of bacterial endotoxins or inflammatory mediators.[54]

Ureteral Histology

Alterations in ureteral histology are likely to have a significant impact on ureteral function. Lee and colleagues evaluated the histology of obstructed and refluxing megaureters and identified marked differences between the two groups. The authors found that refluxing megaureters had a twofold increase in the tissue matrix ratio of collagen to smooth muscle when compared with patients with primary obstructed megaureter and controls. This was due to not only an increase in collagen, but also decreased amounts of smooth muscle in the refluxing ureters.[55] The same group of investigators subsequently demonstrated that there was a greater contribution of type III collagen in the refluxing megaureter, and felt that this may play a role in the pathophysiology of the disease.[56] Because type III collagen is a less distensible fiber, it may cause an intrinsically stiffer ureter and play a role in the lower surgical success in the reimplantation of refluxing megaureters.[57,58] The histology of the refluxing ureter associated with prune belly syndrome likewise exhibits significant histological alteration. Ureters frequently are found to have a scarcity of muscle bundles among dense connective tissue.[59]

PATHOLOGIC PROCESSES AFFECTING URETERAL FUNCTION

The two primary pathophysiologic conditions that affect the pediatric ureter include obstruction and VUR. As mentioned in the previous section, infection can itself alter ureteral function. Often, two or three of these conditions may coexist in one patient, as, for example, in the child with posterior urethral valves who suffers from the common combination of bladder dysfunction, VUR, and urinary tract infection.[60]

Ureteral Obstruction

Well-known anatomic causes of ureteral obstruction that result in a compromise of the ureteral lumen include ureterocele, ureteral ectopia, and urinary lithiasis. In contrast, the classic example of a functional obstruction is the primary obstructed megaureter, in which there exists an adynamic segment of distal ureter with adequate ureteral diameter (Figure 35.4).[61] Apart from anatomic or functional obstruction at the UVJ itself, the relationship between ureteral intraluminal pressure and intravesical pressure is important in determining the efficacy of urine passage across the UVJ into the bladder. The ureter has been shown to decompensate when intravesical pressure approaches 40 cm H_2O.[62]

The effects of ureteral obstruction on renal function are numerous and complex. Molecular mediators, including eisocanoids, nitric oxide, endothelin, and the renin–angiotensin system, dramatically affect blood flow and subsequent urine output.[63–66]

After the onset of obstruction, a backup of urine occurs within the urinary collecting system, along with an associated increase in baseline ureteral pressure and an increase in ureteral length and width.[67,68] A transient increase in the amplitude and frequency of the peristaltic contraction waves accompanies these initial dimensional and pressure changes.[69] With time, as the ureter fills with urine, the peristaltic contraction waves become smaller and are unable to coapt the ureteral wall. Urine transport then becomes dependent on hydrostatic forces generated by the kidney.[67]

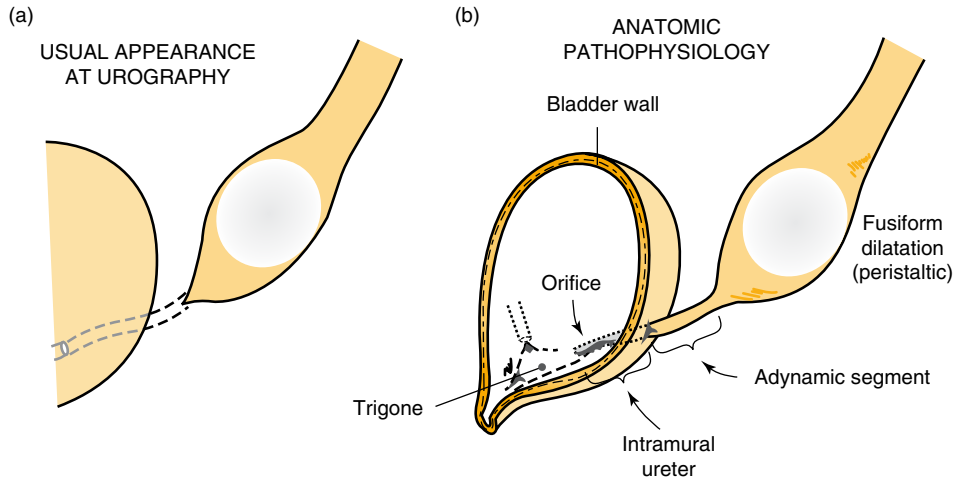

FIGURE 35.4 (a) Graphic representation of a primary obstructed megaureter. Ureteral dilatation begins above the UVJ, usually a few millimeters or more above the bladder, just proximal to an adynamic distal segment of the ureter. (b) Characteristic appearance of the distal portion of a primary obstructed megaureter.

Within a few hours of the onset of obstruction, the intraluminal baseline ureteral pressure increases substantially. With time, the ureter experiences muscular hypertrophy and a greater ability to generate contractile forces.[70,71] Nevertheless, the simultaneous increase in ureteral diameter decreases the ability of the ureters to generate intraluminal pressure, as predicted by the law of Laplace. After ureteral dilatation has occurred, intraureteral pressure declines to a level only slightly higher than the normal baseline pressure. The decrease in ureteral pressure can also be attributed to changes in intrarenal hemodynamics, such as a reduction in renal blood flow, with resultant decreases in the glomerular filtration rate and intratubular hydrostatic pressure.[72,73] Fluid reabsorption into the venous and lymphatic systems (pyelovenous and pyelolymphatic backflow) may also play a role in the reduction in baseline ureteral intraluminal pressure.[74]

Under conditions of obstruction, the hierarchical order of the ureteral pacemakers may also be altered.[75,76] When these alternate pacemakers fire, electrical activity and subsequent peristalsis can propagate both caudally and cranially from the site at which it is initiated. This lack of coordination affects the efficiency of urine transport and contributes to upper tract dilatation.

From a therapeutic standpoint, it is important to understand why a tapered megaureter repair may be beneficial once the obstructive element has been removed. The effect of ureteral diameter on the ability to generate effective peristaltic contractions provides the rationale for ureteral tapering in the patient with an increased ureteral size.[77] Although tapering does not alter muscle thickness and the ability of the ureteral fibers to contract, the decrease in radius, according to the Laplace relation, would result in higher intraluminal pressures and a resultant improvement in antegrade urine transport.

Vesicoureteral Reflux

VUR, the retrograde flow of urine across the UVJ, is the most common problem of the ureter treated by the pediatric urologist.[78] The high incidence of sibling VUR supports a genetic basis for this disorder. Factors that have been implicated in the development of VUR include (1) anatomic and functional abnormalities of the UVJ, (2) inordinately high intravesical pressures, and (3) impaired ureteral function.

Genetics of Reflux

Very strong evidence exists to support a genetic component to VUR.[79,80] Although autosomal recessive, x-linked, and polygenic modes of transmission have been supported by various authors in the past, the majority of data suggest an autosomal dominant pattern of inheritance with variable penetrance.[81] Supporting data include an approximate 50% incidence of sibling reflux in the first 2 years of life and a high incidence of parent-to-child transmission.[80,82] Perhaps most suggestive of autosomal dominant transmission is the incidence of sibling reflux found in multiple-gestation births. Kaefer et al. demonstrated reflux in 80% of identical twins and 35% of fraternal twins.[83] The incidence for groups of twins less than age 18 months was 100% for identical twins and 50% for fraternal twins. Despite such a strong genetic component, it still remains unclear as to which of the factors contributing to reflux is primarily affected (i.e., anatomic properties of UVJ, bladder properties, or impaired ureteral function).

Anatomic Abnormalities of the UVJ

As outlined in the previous section on normal ureteral function, unidirectional flow of urine across the UVJ appears to depend on both passive and active components. In comparing the anatomy of children with and without VUR, Paquin demonstrated that there was a significant difference in the ratio of ureteral tunnel length to orifice diameter between the two groups. Whereas the patients with reflux had a ratio of 1.4:1, children not exhibiting reflux had a significantly longer intravesical tunnel with an average length-to-width ratio of 5:1.[32] Hutch estimated the average intravesical ureter length to be 0.5 cm in neonates and 1.3 cm in adults.[84] Although the 5:1 ratio sets the standard for reimplantation surgery, many pediatric

urologists feel that achieving such a long intravesical tunnel may not be absolutely necessary to obviate reflux.

Lateral displacement of the ureteral orifice is a result of the ureteric bud originating on the mesonephric duct at a point more caudal than normal. As a result, the period during which the orifice undergoes migration is prolonged. As predicted by Stephens, the orifice will eventually assume a position on the trigone that is more lateral than usual. The ureter will have a submucosal course that is short and almost perpendicular to the bladder wall, thus failing to meet the anatomic requirements needed for proper functioning of the flap valve mechanism.[85,86] The degree of reflux correlates with the degree of laterality and inversely with the length of the submucosal ureter (Figure 35.5). Spontaneous resolution of reflux in children is in part explained by the growth of the bladder, during which the submucosal tunnel elongates.[85]

Proper formation of the trigone is also believed to be necessary to provide adequate muscular support of the ureters. A more caudal takeoff of the ureteric bud from the mesonephric duct results in a shorter common excretory duct. As a result, its contribution to the development of the trigone is decreased, resulting in poor muscularization. The importance of adequate muscular backing is underscored by the rare female patient with bilateral single-system ectopic ureters. When reimplanting a ureter in these children, special attention must be taken to achieve very long tunnel length due to absent trigonal musculature and poor detrusor muscularization, both of which result in poor posterior support for the reimplanted ureter. If special care is not taken to achieve a greater than normal ureteral tunnel length, these patients are prone to postoperative reflux.[87] Focal absence of adequate muscle backing in the form of a periureteral diverticulum can also contribute to VUR due to poor muscle backing and poor attachment of the ureter to the trigonal muscle complex.[88]

Alterations in the active valvular mechanism may also occur and result in or contribute to the expression of the reflux phenotype. From an embryologic standpoint, a more caudal takeoff of the ureteric bud from the mesonephric duct and the earlier absorption into the bladder would allow less time for the common mesenchyme to accumulate around the developing ureteric bud. One would therefore anticipate that the intramural ureter may be deficient in musculature. As a result, the orifice can be patulous or gaping.

Recent histologic evaluation of the distal ureters in children with VUR has suggested that there may be dysplasia, atrophy, and architectural derangement of smooth muscle fibers.[89] In addition, there appears to be altered extracellular matrix deposition and a decrease in intramural nerve supply.[90] This combination of factors, by affecting the muscle layer of the intramural ureters, may alter the active valvular mechanism deemed by many to contribute to the function of the UVJ. The fact that many children outgrow their VUR suggests that even if histological alterations of the intravesical ureters are contributing to the presence of VUR, they play only a partial role in the reflux phenotype.

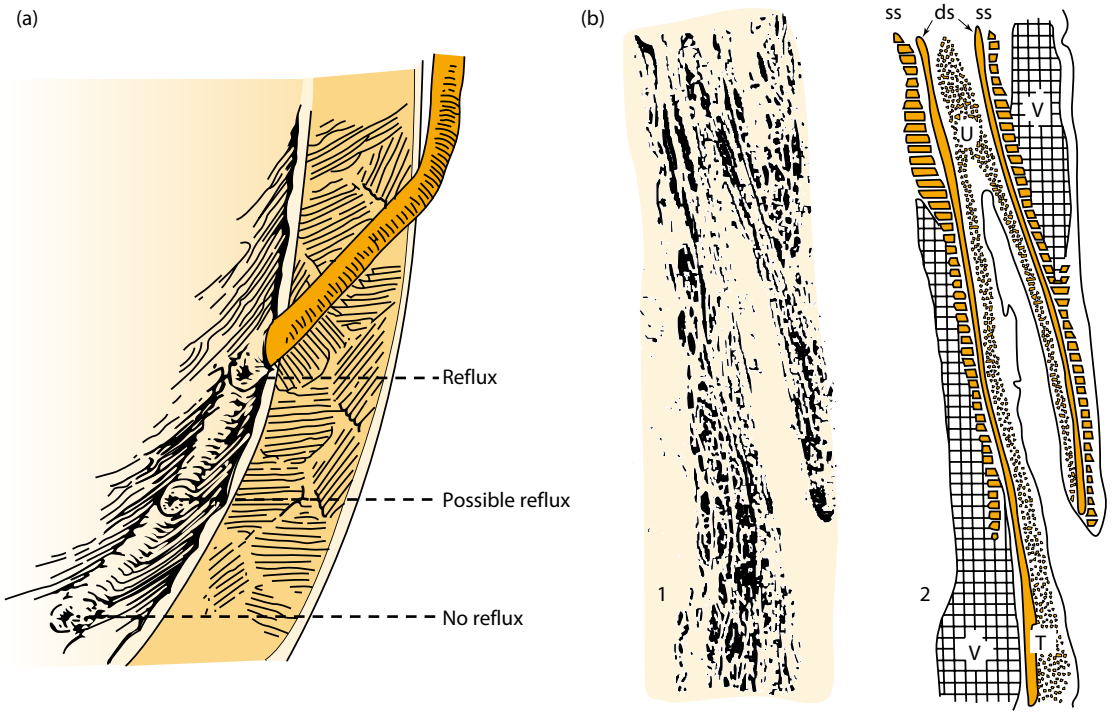

FIGURE 35.5 (a) The refluxing UVJ has an inadequate length of intravesical submucosal ureter. Some orifices with marginal submucosal tunnels may reflux intermittently. (b) UVJ in longitudinal section: 1, photomicrograph; 2, diagrammatic representation. The ureteral muscularis (U) is surrounded by superficial (ss) and deep (ds) periureteral sheaths, which extend in the roof of the submucosal segment and continue beyond the orifice into the trigonal muscle (T). The relationship of superficial sheath to the vesical muscularis (V) is clearly seen. Transverse fascicles in the superior lip of the ureteral orifice belong to the superficial and deep sheaths. No true space separates ureter from bladder. ([a] Adapted from Glenn J., ed., *Urologic Surgery*, 2nd edn., Harper & Row, New York, 1975; [b] Adapted from Elbadawi A. *J Urol* 1972;107:224–9.)

Intravesical Pressure

As mentioned earlier in this chapter, intravesical pressure must be lower than the pressure generated by the ureter in order for there to be adequate transport of urine in an antegrade direction. In the presence of increased intravesical pressure, secondary reflux can occur.[62] Failure to maintain a low intravesical pressure also results in an increase in the incidence of VUR. This is commonly referred to as secondary reflux. The most common anatomic cause of secondary VUR is posterior urethral valves, in which approximately 50% of boys are affected.[91,92] However, functional causes of increased intravesical pressure, including detrusor sphincter dyssynergia in patients with neuropathic bladder dysfunction secondary to myelomeningocele, are far more common.[93]

Transient urodynamic abnormalities have also been identified in neurologically normal children who present with urinary tract infections and reflux in the first year of life. One study identified abnormalities, including detrusor hyperreflexia and elevated filling pressures, in 97% of boys and 77% of girls who presented in infancy with reflux.[94,95] Intravesical pressures in boys were found to be higher than in girls, a finding confirmed by other investigators.[96,97] This finding may account for gender differences in the degree of reflux. In older children, bladder dysfunction is typically an acquired phenomenon resulting from abnormal voiding patterns in neurologically normal children.[98,99]

The normal UVJ is extremely resistant to reflux, even in the face of very high intravesical pressures that occur with normal voiding. However, if intravesical pressures remain chronically elevated, the antireflux mechanism can be overcome. McGuire et al. demonstrated that if intravesical pressures exceed 40 cm H_2O, the incidence of reflux and renal injury increases.[62] The development of reflux further reduces the efficiency of bladder emptying, leading to further increases in intravesical pressures and yet further damage to the upper urinary tract.[100]

Impaired Ureteral Function

Although an abnormality of the UVJ is the primary etiologic factor in most cases of VUR, evidence exists that decreased ureteral peristalsis can be a contributory factor. This may explain why a normal ureter may not reflux even when reimplanted into a bladder without a submucosal tunnel, or why a defunctionalized refluxing ureter may cease to reflux when a proximal diversion is taken down.[101–103] Tanagho's observation that VUR may temporarily cease after ureteral electric stimulation further supports this possibility.[104]

Even the mildest forms of VUR may be associated with a decreased frequency of ureteral peristalsis.[105] Although this may offer further evidence that decreased peristaltic activity is a possible etiologic factor in the development of reflux, an alternative interpretation is that the decreased peristaltic activity reflects changes in ureteral or renal function resulting from the reflux. Finally, the success rate of antireflux procedures is lower with poorly functioning dilated ureters. Although this may be related to technical factors, decreased peristaltic activity may be another reason for the lower success rate in this condition. Bladder infections and the accompanying inflammation may also contribute to reflux by decreasing the compliance of both the bladder and intramural ureter, elevating intravesical pressures, and distorting and weakening the UVJ.[106–108] In some patients, reflux appears to occur only during episodes of acute cystitis and resolves once the infection has been adequately treated and the inflammatory response has resolved.[109]

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CHAPTER 36

Ureteral Development

Steven E. Lerman, Irene M. McAleer, Alan L. Kaplan, and George W. Kaplan

Ureteral development from the ureteral bud is closely associated with the distal end of the mesonephric duct, also known as the Wolffian duct. As described in Chapter 20, the mesonephric duct bends ventrally as it enters the cloaca. In the fifth week, there is an outpouching (the ureteral bud) from the dorsal medial aspect of the bend.[1] This is the beginning of the ureter. As originally shown by Grobstein, signals from the metanephric blastema induce elongation of the ureteric bud and invasion of the blastema by the ureteral bud.[2] Evidence in both mice and humans is helping to explain the mechanisms by which this occurs, but our understanding is still incomplete. The renin–angiotensin system (RAS), which in postnatal life regulates blood pressure, is a key factor in the development of the ureteral bud and subsequent branching of the ureter to produce the renal pelvis and the calyces.[3] Angiotensin I is converted to angiotensin II by the angiotensin-converting enzyme (ACE). Angiotensin II acts via AT_1R and AT_2R (angiotensin receptors) to induce the production of the glial-derived neurotrophic factor (GDNF) in the metanephric blastema. GDNF in turn acts on the tip of the ureteral bud via interaction with the ret (rearranged during transfection) receptor tyrosine kinase and Gfralpha1 (glial cell line–derived neurotrophic factor receptor alpha) to cause cell proliferation, elongation of the ureter, invasion of the metanephric blastema, and eventual branching of the ureter.[4] The entire length of the Wolffian duct can respond to GDNF. Consequently, regulation of the site of GDNF activity is critical to the production of normally situated ureteral orifices.[5] The distal end of the mesonephric duct inferior to the ureteral bud opening forms the common excretory duct. The trigone has been thought to be formed by integrating the upper portions of the common excretory ducts and a small portion of the mesonephric ducts just superior to the ureteral bud into the bladder base (Figure 36.1). Studies by Tanaka et al. have cast doubt on this theory and have suggested that the trigone is formed from endoderm rather than mesoderm.[6] Ultimately, with expansion and absorption of the common excretory duct into the trigone or its loss due to apoptosis and replacement by endoderm, ureteral and Wolffian duct orifices become separated from each other.

In mice, mutations that result in the absence of GDNF, Ret, or Gfralpha1 cause bilateral renal aplasia due to a failure of the ureteric bud to grow.[7] The development of ureteral atresia is thought to be due to relative or total ischemia that might occur with the migration of the developing kidney as it changes and reestablishes regional blood supply to the ureter. This theory is based on experimental studies on intestinal atresia.[8] It may be extrapolated to explain ureteral stenosis and postnatal involution of multicystic dysplastic kidneys.

Complete or partial ureteral duplication (or triplication) can occur if multiple ureteral buds develop, or if the ureteral bud divides before meeting the metanephrogenic mass. In this instance, if one bud met the center of the metanephrogenic mass and the other a pole of degenerating metanephric tissue, the former would develop normally, whereas the latter might be dysplastic (Figure 36.2). This seems to explain the high association of dysplasia with ureteral ectopia,[9] although these ureters are also often obstructed.

PAX2 (paired box gene 2) is a positive regulator of GDNF, while Spry1 (sprout gene1) and Bmp4 (bone morphogenic protein 4) are inhibitors of GDNF. A delay or absence in RET signaling can produce ectopic ureters, while mutations in genes from Bmp4 and components of the RAS cascade can produce vesicoureteral reflux. Other factors involved in ectopic budding of the ureteral bud are fibroblast growth factors 7 and 10 and their receptor FGFR2. These observations confirm the observations of Mackie and Stephens that abnormal ureteral bud position induces renal dysplasia.[5]

Ureteral ectopy occurs when the orifice is located in a location other than the normal orthotopic corner of the trigone. These orifices can be within the bladder, urethra, vas, or vagina. Ureteral ectopy is four times more common with duplicated systems than with single ureteral systems.

Ureteral obstructions occur primarily at the ureteropelvic and ureterovesical junctions but can also occur in the pelvis where the ureter crosses over the iliac vessels. These obstructions are usually intrinsic in nature, and the area in question is often of normal caliber but abnormally fibrous histologically, perhaps reflecting a localized vascular accident sometime during development (Figure 36.3). The elongating ureter is formed only of epithelial cells, but muscle is induced to form from the surrounding mesenchyme by Shh (Sonic hedgehog) signals.[10] One might speculate that abnormalities in this signaling could produce obstructions, such as ureteropelvic junction obstructions and obstructive or nonobstructive megaureter.

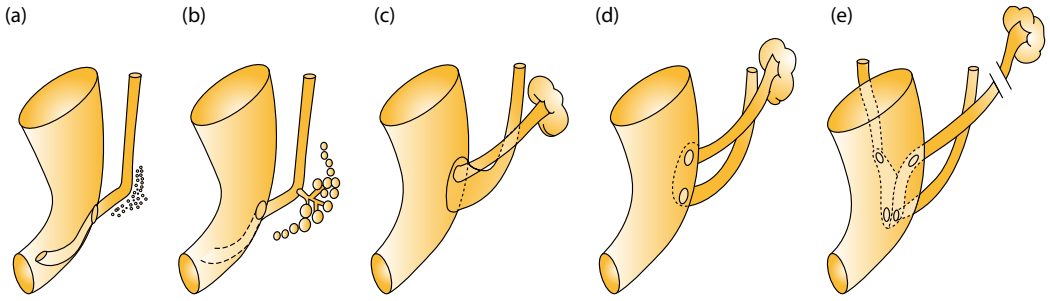

FIGURE 36.1 Absorption of the terminal end of the Wolffian duct. Diagram to demonstrate the absorption of the terminal end of the Wolffian duct and the ureter into the urethra and bladder. (a and b) Relocation of orifice from original site adjacent to cloacal membrane to upper urethra. (b) Ureteric bud arises from the elbow bend of the Wolffian duct and penetrates the contiguous renal blastema. (c) Trumpet expansion of duct up to and a little distance beyond the bud which rotates laterally to an anterior position on the duct. (d) Further expansion and separation of ureter from Wolffian duct. (e) Orifices of ureter and Wolffian duct (vas deferens) in corner of trigone and urethra, respectively. (Reproduced from Stephens FD. *Congenital Malformations of the Urinary Tract*. New York: Praeger, 1983. With permission; also with permission from Professor Stephens.)

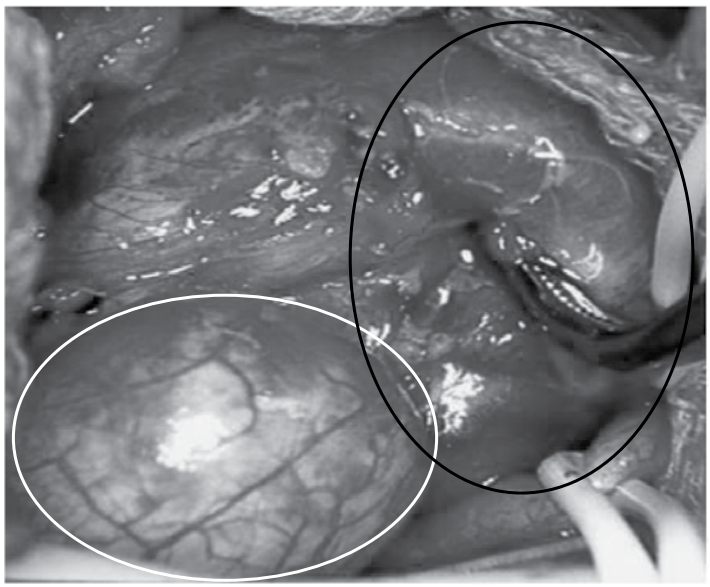

FIGURE 36.2 Dysplastic cystic upper pole (white oval) with normal lower pole (black oval) on left kidney with ectopic obstructed upper pole ureter.

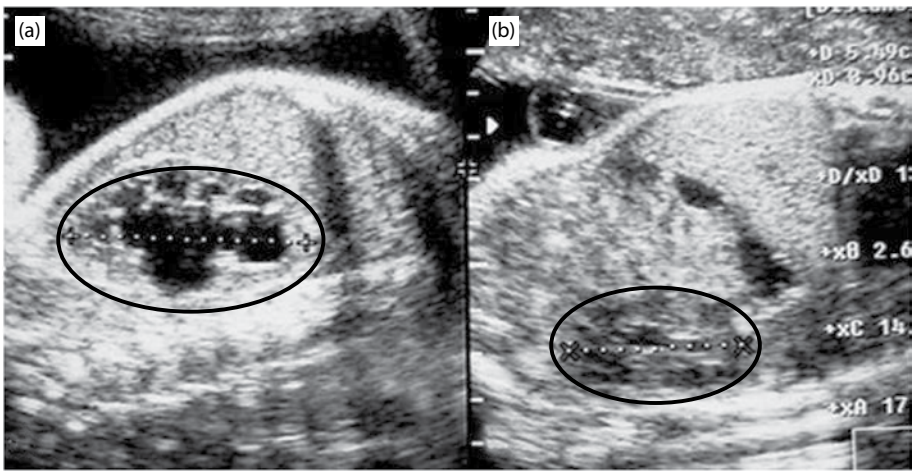

FIGURE 36.3 (a and b) Bilateral hydronephrosis at 28 weeks' gestation, suggesting possible obstruction at ureteropelvic junction on (a) (ovals around kidneys).

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CHAPTER
37

The Imaging of Vesicoureteral Reflux and Ureteral Disease

David A. Diamond, Jeanne S. Chow, and Frederick D. Grant

INTRODUCTION: THE IMAGING OF REFLUX AND URETERAL DISEASE

This chapter discusses the imaging techniques used in evaluating vesicoureteral reflux and ureteral diseases. Different imaging modalities are described with specific clinical scenarios to highlight the uses of each modality. Practice patterns may vary from institution to institution.

IMAGING VESICOURETERAL REFLUX

Voiding cystourethrography (VCUG), radionuclide cystography (RNC), and sonocystography demonstrate the presence or absence of vesicoureteral reflux. While VCUG is a fluoroscopic examination and RNC is a nuclear medicine study, studies are performed similarly and expose the patient to ionizing radiation. Sonocystography is performed with ultrasound and exposes the child to no ionizing radiation.

During VCUG, dilute water-soluble contrast is instilled into the bladder through a sterile urethral catheter by gravity under fluoroscopic guidance. Spot images of the abdomen, early filling views of the bladder, oblique images of the bladder to view the ureterovesical junctions (UVJs), oblique views of the urethra (especially important in boys), and postvoid images of the abdomen are standard. Additional views to show other abnormalities may be necessary (Figure 37.1a–f).

In infants, a cyclic study is performed, where the bladder is refilled with contrast after the infant voids around the catheter to increase the sensitivity of the study.[1] Otherwise, the bladder is filled to the predicted capacity to maximize the likelihood for finding reflux. Bladder capacity can be calculated by the two following sets of equations:[2,3]

- Under a year of age:

$$\text{Bladder capacity (mL)} = \text{Weight in kg} \times 7$$

- Older than a year of age:

$$\text{Bladder capacity (oz.)} = (\text{Age in years} + 2) \times 30$$

The relationship of normal bladder capacity and age in children has been found to follow a nonlinear curve[4] and can be determined for two age groups:

- For children under 2 years of age:

$$2 \times \text{Age (years)} + 2 = \text{Capacity in oz.}$$

- For children over 2 years of age:

$$\text{Age in years}/2 + 6 = \text{Capacity in oz.}$$

Direct RNC uses the instillation of radiolabeled fluid into the urinary bladder to demonstrate vesicoureteral reflux. Like in VCUG, a urethral catheter is inserted after the patient voids and the perineum has been prepped. The usual radiotracer is [^{99m}Tc]-sodium pertechnetate, but if there is a history of bladder augmentation with gastric or intestinal mucosa, then ^{99m}Tc-labeled sulfur colloid is preferred to limit mucosal absorption of free pertechnetate. Although some guidelines[5] suggest a weight-based radiopharmaceutical dose, the currently recommended tracer dose is 0.5–1.0 mCi[6] to ensure adequate sensitivity of the study.

Using a gamma camera, dynamic images are acquired in the posterior projection. A radiopharmaceutical is administered aseptically into the bladder and followed by warm saline infused by gravity flow. Infusion is continued until the end of the filling phase, indicated by slowing or stopping of flow, or the infused volume reaches a bladder volume appropriate for age. If the patient has not begun to void spontaneously, he or she is urged to void. Dynamic imaging should continue during voiding, as many cases of reflux will be identified only during the voiding phase. Some patients may be unable to void while supine, and it may help to have them sit upright (preferably while still imaging) or sit on a toilet or commode. Vesicoureteral reflux identified by RNC is typically graded on a 3-point scale (Figure 37.2).[7] A postvoid image of the kidneys and bladder may be helpful to demonstrate reflux that occurs during delayed voiding. In patients with demonstrated reflux, a postvoid image is useful for identifying postvoid retention of the tracer in the renal collecting system, which may suggest some degree of ureteral obstruction superimposed on the vesicoureteral reflux. Some guidelines suggest completely emptying the bladder through a urethral catheter to minimize radiation exposure from the tracer retained in the bladder.[5] Although a cyclic study can be performed with RNC, the yield of

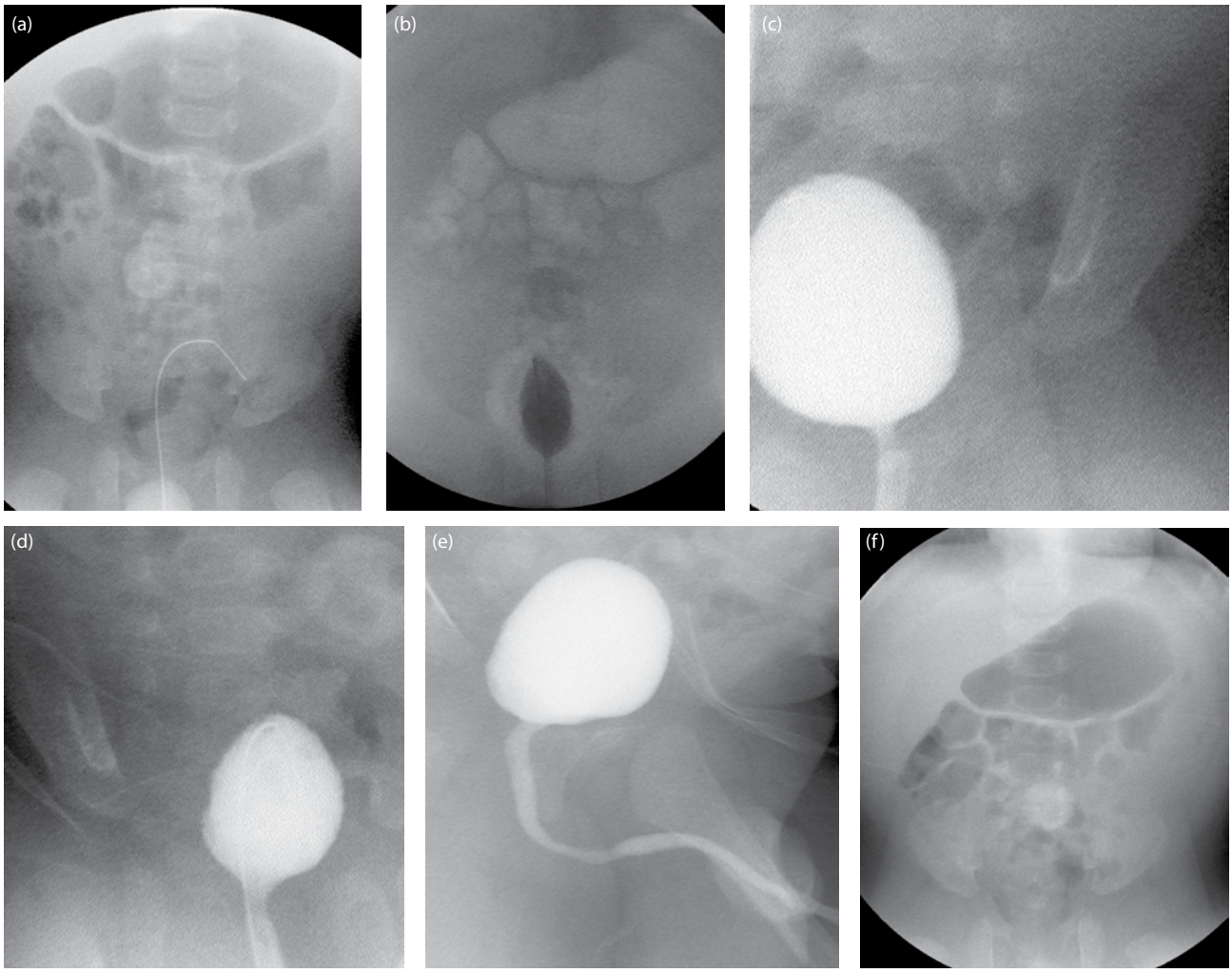


FIGURE 37.1 Standard images from normal VCUG in a boy include (a) a scout film of the abdomen and pelvis, (b) an early filling view of the bladder, (c and d) bilateral oblique views to visualize the UVJs, (e) an oblique view of the male urethra, and (f) a postprocedure image of the abdomen and pelvis.

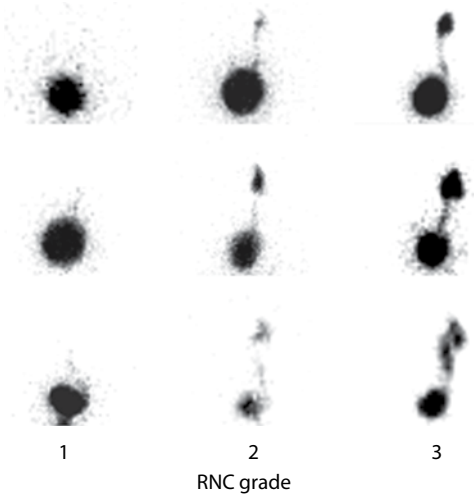


FIGURE 37.2 RNC grading. When diagnosed by RNC, the severity of vesicoureteral reflux is graded on a 3-point scale: grade 1, reflux only into the ureter; grade 2, reflux into the renal collecting system; and grade 3, reflux into a tortuous ureter or dilated renal collecting system.

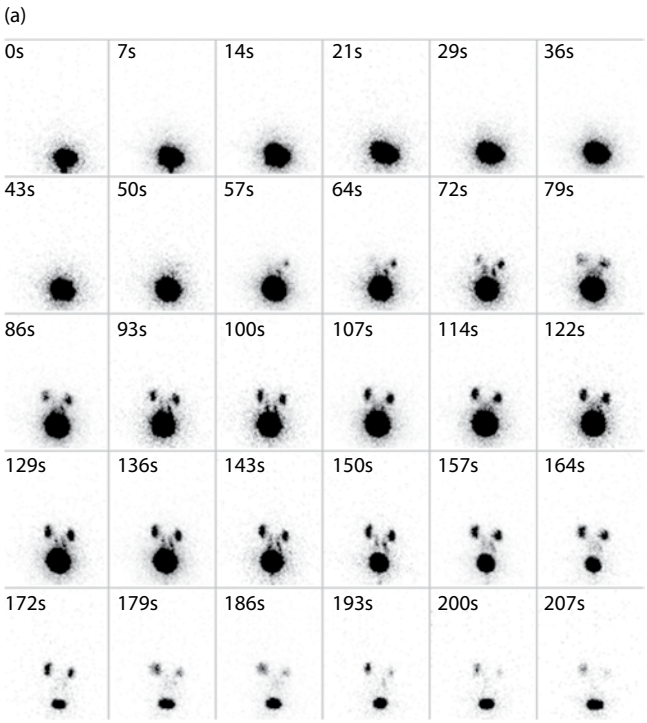
repeated infusion is quite low, possibly due to the high sensitivity of the study for subtle reflux.

Bladder volumes and pressures can be recorded during the performance of RNC.[5,8,9] The patient should void before the study, and the residual urine volume can be measured at the time of catheter insertion. The volume of infusate provides an estimate of bladder volume, and the void volume also can be measured. At our institution, a single-head gamma camera installed in the urology suite allows RNC to be performed during urodynamic studies, thereby preventing the need for the patient to undergo a second urethral catheterization.

Both VCUG and RNC expose the patient to low doses of ionizing radiation, and all studies should be performed in accordance with the ALARA (as low as reasonably achievable) principle. Traditional VCUG exposes the patient to 100 times the radiation of RNC. In the past two decades, low-dose fluoroscopy techniques, including digital fluoroscopy and pulse fluoroscopy, have decreased radiation dose to the patient[10–14] while still providing diagnostic quality images.[15–17] Gonadal shielding and careful image coning also substantially decrease patient radiation

exposure. In our department, modern low-dose fluoroscopic methods have reduced the radiation dose of VCUG to approximately eight times that of RNC,[18] but doses vary from hospital to hospital.

The decision to perform RNC or VCUG on a patient suspected to have reflux depends on the patient, clinical indication, and referring physician. When VCUG and RNC are compared, VCUG provides greater anatomical detail at the expense of a higher radiation dose than RNC (Figure 37.3a and b). VCUG allows evaluation of the bladder wall, UVJ (in patients with reflux), intrarenal reflux, and male urethra (Figure 37.4). RNC may be more sensitive for subtle reflux, but does not provide the anatomic detail provided by VCUG. Therefore, in our institution VCUG is typically performed for the initial evaluation of males and young children or infants with well-documented pyelonephritis; patients with neurogenic bladder; patients with duplex kidneys (Figure 37.5) and



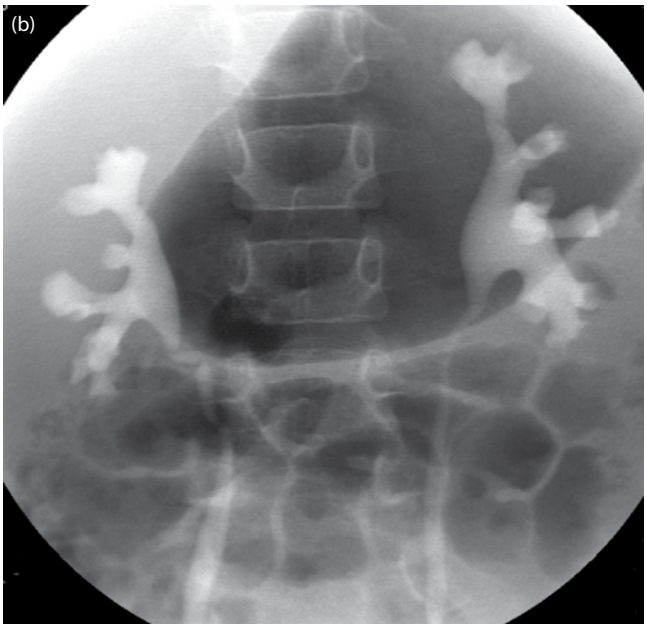


FIGURE 37.3 (a) Multiple images from a radionuclide cystogram demonstrate bilateral grade 2 reflux. (b) A single image from VCUG demonstrates bilateral grade 2 or 3 reflux.

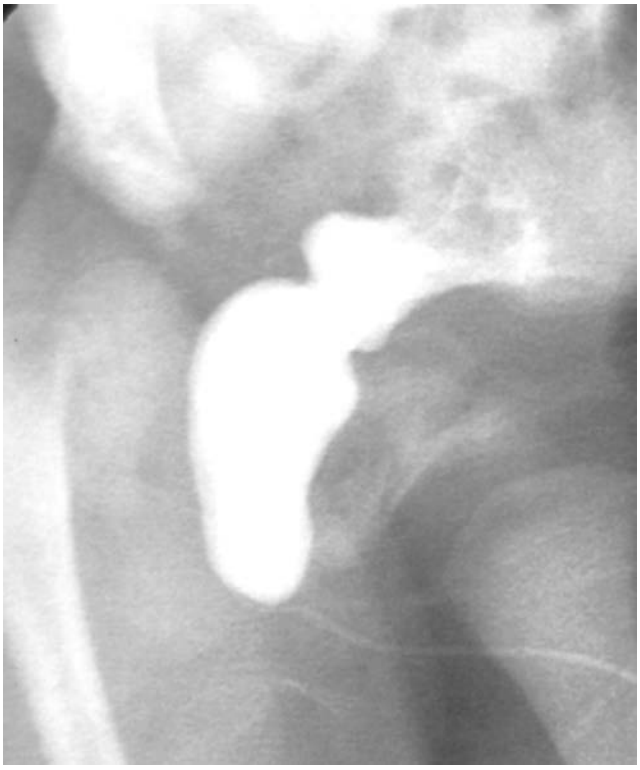


FIGURE 37.4 Voiding cystourethrogram showing posterior urethral valves and dilatation of the posterior urethra. This image emphasizes the importance of evaluating the male urethra during VCUG.

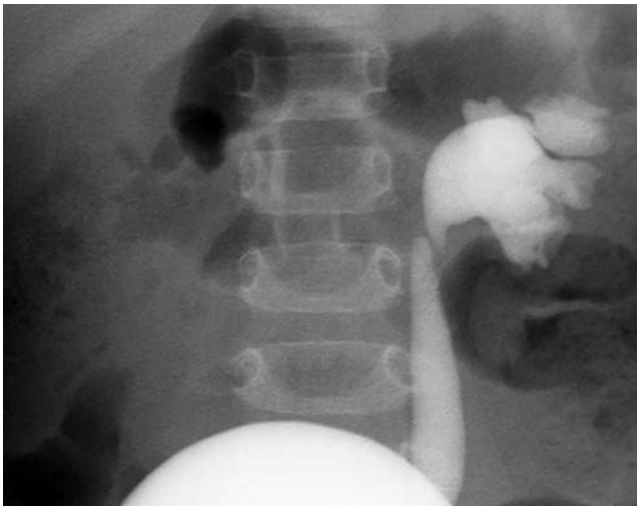


FIGURE 37.5 Voiding cystourethrogram showing grade 2 or 3 left lower-pole reflux. The orientation of the calyces is toward the ipsilateral shoulder.

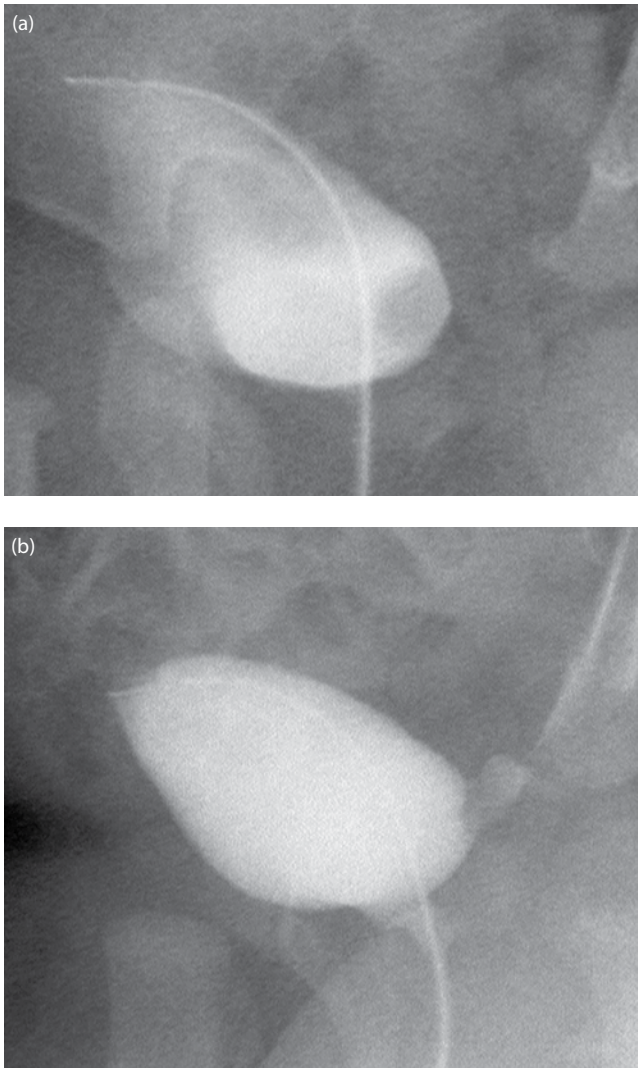


FIGURE 37.6 Oblique VCUG images of showing a left ureterocele (a) that everts (b).

dilatation of the upper or lower pole, or both; and patients suspected to have a ureterocele (Figure 37.6a and b).

RNC is performed for the follow-up of patients in whom reflux has been identified by VCUG, after antireflux surgery, and may be used in the initial evaluation of older girls. In siblings of children with reflux, the prevalence of reflux may be as high as 50%. Until recently, these siblings were screened for reflux, usually by RNC. This practice has recently come into question, partly on economic grounds,[19] and the clinical utility of screening siblings for reflux is an unresolved issue.

During sonocystography, the bladder is infused with an ultrasound contrast agent, and reflux is assessed by the sonographic appearance of contrast within the kidneys and ureters. The grading system is similar to that for VCUG.[20] Sonocystography is more sensitive[21] and accurate in detecting reflux[22–24] and provides similar anatomic detail of the bladder, ureters, and urethra as VCUG.[25,26] It is indicated in the first-time evaluation of reflux in girls and follow-up reflux after VCUG in boys and girls[27] and screening in high-risk patients. Transperineal ultrasound during voiding can detect posterior urethral valves[28] and is used to evaluate the urethra confidently.[29] At the time of this publication, ultrasound contrast agents were not approved by the U.S. Food and Drug Administration (FDA) for sonocystography, thus limiting its use there.

Cystography for assessing reflux can be stressful for the patient and family and is ideally performed by an experienced clinician in an environment comfortable for the patient, family, and healthcare provider. When parents and children are also well informed, prepared, and reassured, the discomfort of the examination is compared to that of an immunization, and thus no sedation is necessary.[30] Trained technologists and child life specialists are very helpful in preparing, educating, and reassuring parents and patients.[31] It can be helpful if a technologist, nurse, or child life specialist speaks with a parent by telephone a few days before the scheduled study. In the rare circumstances when sedation is required, midazolam and nitrous oxide can be used without decreasing the reliability of the examination.[32–35]

Patients who are suspected to have reflux because of a well-documented case of pyelonephritis should receive prophylactic antibiotics until the examination, and antibiotics should be continued if reflux is found.[36] Use of prophylactic antibiotics for prenatal hydronephrosis or a family history of reflux is controversial. Patients with prior allergies to intravenous contrast do not have allergies to intravesical contrast; thus, no premedication is required.

Renal Cortical Scintigraphy

Renal cortical scintigraphy uses the radiopharmaceutical ^{99m}Tc–dimercaptosuccinic acid (DMSA) to provide functional images of the renal cortex.[37] After intravenous administration, ^{99m}Tc-DMSA is taken up by cells in the proximal renal tubule, with little ^{99m}Tc-DMSA excreted into the renal collecting system. After 3–4 hours, most administered tracers will have cleared from the systemic circulation and accumulated in the renal cortex. The North American consensus guidelines[6] recommend an administered dose of ^{99m}Tc-DMSA of 1.85 MBq/kg (0.05 mCi/kg), with a minimum dose of 18.5 MBq (1.0 mCi).

Planar images (acquired in the posterior projection) permit localization of both kidneys and assessment of renal size and configuration. Images acquired in the posterior and oblique projections with a pinhole collimator can provide more detail about renal cortical structure and will provide greater sensitivity for identifying scars and other defects in the renal cortex. Single-photon emission computed tomography (SPECT) improves both the sensitivity and specificity for identifying defects in the renal cortex. In children less than 1 year of age, small patient size usually limits the utility of SPECT for imaging the renal cortex. Infants may have persistent fetal lobation, which an inexperienced interpreter may confuse with renal scarring. SPECT also offers the possibility of quantitative assessment of the functional renal volume.[38]

In patients with acute pyelonephritis, renal cortical imaging will demonstrate diminished DMSA uptake in the involved regions of the renal cortex. However, the use

of DMSA in the setting of acute infection will have little utility if all febrile urinary tract infections are treated in a similar manner. Renal cortical scintigraphy has greater utility when used for the evaluation of postinfection renal scarring. With successful therapy of pyelonephritis, long-term damage to the renal cortex can be averted, and this will be demonstrated by resolution of the cortical defects identified by cortical scintigraphy. Typically, scintigraphic defects will resolve within 3–6 months of an infection.[39] However, one study showed additional resolution for up to 3 years after treatment of an acute infection.[40] Scintigraphic defects will not resolve when there is persistent postinfection scarring. In one recent systematic review,[41] among children with an initial episode of febrile urinary tract infection, 57% were reported to have abnormalities on an acute DMSA scan and 15% were reported to have persistent abnormalities consistent with cortical scarring on a follow-up DMSA scan performed at least 5 months after the first scan. Patients with reflux were at higher risk for developing pyelonephritis and were more likely to develop renal scarring.

In patients with the diagnosis of reflux, DMSA cortical scintigraphy can be useful to assess for renal cortical scarring. Patients with both reflux and renal scarring may be at greater risk of additional scarring,[42] and the presence of scarring may support earlier surgical intervention to correct the reflux. No studies have adequately compared the accuracy of DMSA SPECT and state-of-the-art ultrasound in the evaluation of renal cortical scarring.

The standard approach for the evaluation of an initial febrile urinary infection[36] has been referred to as the "bottom-up" approach. That is, patients presenting with a febrile urinary infection are evaluated for reflux, which can be treated medically or surgically. In some patients, renal imaging, with either ultrasound or renal cortical scintigraphy, can be used to assess the risk of renal scarring. Critics of this approach point out that it will miss the small subset of children that may develop renal scarring in the absence of diagnosed reflux, and that many children with reflux will never develop renal scarring.[43] In response to these concerns, a "top-down" approach has been proposed, and has seen greater adoption in Europe than the United States.[44,45] This approach is based on the principle that abnormal DMSA cortical scintigraphy during an acute urinary infection identifies kidneys at risk for subsequent renal scarring. In the absence of a renal cortical defect, a patient with an acute febrile urinary infection will receive antibiotic therapy, but will undergo no further evaluation. Only patients with a renal cortical defect are evaluated for reflux. Critics of the top-down approach point out that a patient will not undergo evaluation for reflux until renal damage may already have developed. Also, implementation of the top-down approach requires DMSA cortical scintigraphy to be performed within 72 hours of the onset of acute urinary tract infection symptoms, which can be inconvenient and disruptive for the patient and family. The appropriate evaluation and management of children with a febrile urinary tract infection remains controversial[36,46,47] and is unlikely to be settled without rigorous studies assessing risk and outcome to provide evidence-based recommendations.[48]

IMAGING OF URETERAL DISEASES

Ultrasound

Introduction

Ultrasound is typically the first study selected in evaluating potential ureteral disease in children because it is noninvasive, rarely requires sedation, and emits no ionizing radiation. Whereas the normal-caliber ureter is not routinely visualized on ultrasound, even a mildly dilated ureter is readily imaged with contemporary equipment. This makes ultrasound an ideal modality for following anatomical abnormalities or pathological processes that result in hydronephrosis and hydroureter. Other than ideally having a bladder fully distended with urine to evaluate the bladder and distal ureters, no patient preparation is necessary.

The diagnostic quality of the ultrasound depends on the ability of the sonographer and sonologist, the machinery, and the use of new techniques and software. Imagers trained to work with children often employ special tricks when scanning children, such as prone imaging or scanning while the patient is being cradled by a caretaker, to obtain the best images.

The newest ultrasound machines offer a variety of methods that improve image quality over conventional imaging. For example, spatial compound imaging, or simply compound imaging, is a method that obtains information from several different angles of insonation and combines them to produce a single image. Harmonic imaging exploits nonlinear propagation of sound waves to form a more focused ultrasound beam that is less susceptible to reverberation artifacts. Ultrasounds are also able to acquire a volume of information, which can be translated into three-dimensional images and four-dimensional movies.[49]

The kidneys and bladder are easily visualized by ultrasound. Viewing the kidneys in the supine and prone positions increases the likelihood of visualizing the entire kidney, which can be partially obscured by bowel gas. A normal ureter is usually collapsed, and not typically visualized by ultrasound. A peristalsing ureter containing urine, measuring up to 3.5 mm in diameter, is normal. Dilated ureters are easiest to visualize near the ureteropelvic junction (UPJ) and behind a full bladder near the UVJ. The midureter is often hidden by bowel when imaged from the supine approach, and coronal imaging through the retroperitoneum can be helpful. A nonobstructed collecting system may be dilated due to a full bladder and should be reevaluated after the bladder is emptied.

Hydroureter is typically implied by seeing proximal and distal ureteral dilatation even when the midureter is obscured by bowel gas. Hydroureter may be due to reflux or obstruction, or both. The degree of distal ureteral dilatation in patients with reflux predicts a high grade of reflux.[50] In patients with acute obstruction, the absence of a ureteral jet or asymmetry in ureteral jet frequency in the bladder correlates highly with high-grade ureteral obstruction.[51]

Prenatal Hydronephrosis

The finding of hydronephrosis is made on 1 in 200 routine prenatal ultrasounds. Postnatally, ultrasound will confirm the majority of these cases to be mild, without hydroureter, allowing them to be followed sequentially with serial ultrasounds until resolution has been documented. If the postnatal ultrasound demonstrates moderate (characterized by calyceal dilatation) or severe (characterized by parenchymal thinning) hydronephrosis, further diagnostic studies are indicated. These would include VCUG to rule out reflux and magnetic resonance urography (MRU) or a mercaptoacetyltriglycine (MAG-3) renal scan to exclude a UPJ or UVJ obstruction. Hydroureter with any degree of hydronephrosis mandates further evaluation for reflux with VCUG (Figure 37.7a and b).

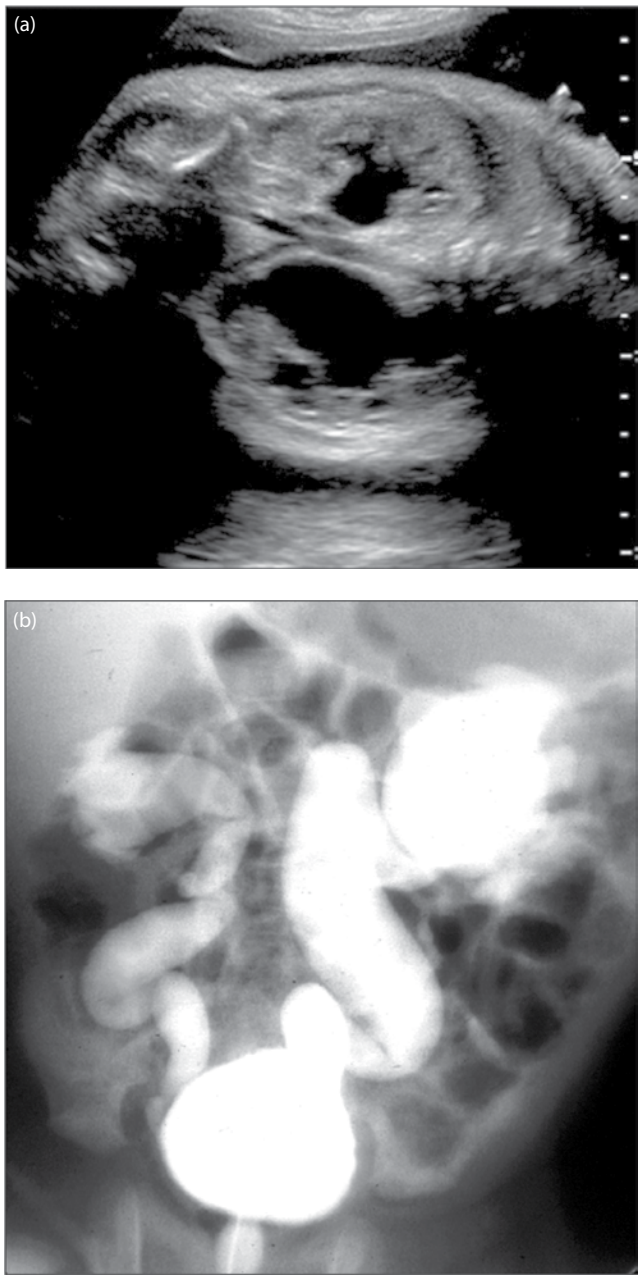


FIGURE 37.7 (a) Prenatal ultrasound showing bilateral hydronephrotic kidneys in the coronal plane. (b) VCUG demonstrates bilateral high-grade vesicoureteral reflux.

Duplex Systems

A duplex collecting system may present prenatally, especially if there is associated hydronephrosis. Hydronephrosis of the upper pole and ureter is typically associated with distal ureteral obstruction due to an ectopic ureter or ectopic ureterocele. Ultrasound views of the bladder enable one to make this distinction. A ureterocele is visualized as a fine septum within the bladder, while an ectopic ureter courses beneath the full thickness of the bladder wall in the transverse view. Lower-pole hydronephrosis is typically due to reflux or UPJ obstruction. Therefore, VCUG and MRU or a MAG-3 renogram is needed for further evaluation of lower-pole hydronephrosis (Figure 37.8a–c).

Postoperative Assessment

In patients undergoing either pyeloplasty for UPJ obstruction or transurethral incision of an obstructing ectopic ureterocele, ultrasound is an ideal modality for postoperative confirmation of the relief of ureteral obstruction. Ultrasound is a nondefinitive study for ruling out postoperative reflux, as it can miss up to 75% of cases of reflux.

Renal Calculi

Ultrasound is an excellent initial study for the assessment of renal colic in the child. Initially, it is important to rule out a congenital obstructive lesion of the ureter at either the UPJ or UVJ. Next, an attempt is made to identify a stone within the ureter, which typically produces distinct shadowing and hydroureteronephrosis proximally. Additional calculi may be imaged within the kidney, and a stone may coexist with a congenital obstructive lesion or alternatively mimic one, if lodged at the UPJ or UVJ. Occasionally, a perinephric urinoma can be imaged in conjunction with an obstructing calculus. Evaluation for a renal stone requires meticulous and thorough imaging, which includes carefully following the entire course of the renal pelvis and ureter (Figure 37.9).

Not only is ultrasound capable of imaging renal and ureteral calculi, but in the form of extracorporeal shock wave lithotripsy (ESWL) with ultrasound guidance, it can also be used to fragment calculi, thereby allowing them to be cleared naturally by the urinary tract. The effectiveness of any surgical treatment for stone clearance may be accurately assessed by ultrasound, and ultrasound may be used for long-term surveillance of stone formers.

Ectopic Ureter

The evaluation of a female patient who is continually wet must include consideration of an ectopic ureter. Ultrasound remains the first imaging evaluation for making this diagnosis, as it may show findings that indicate a (sometimes subtle) dysplastic upper pole or solitary ectopic dysplastic kidney. Traditionally, intravenous pyelography (IVP) was used to evaluate a patient with a suspected ectopic ureter, but this has been essentially replaced by computed tomography urography (CTU) and MRU. These techniques

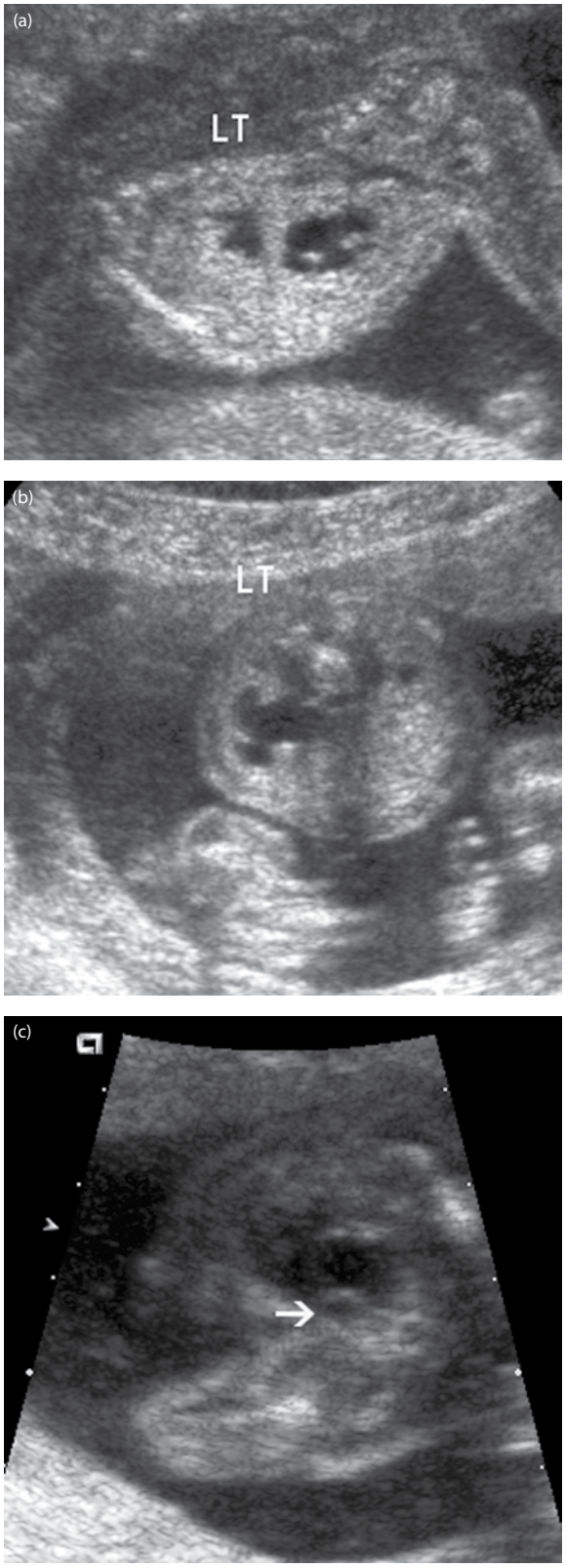


FIGURE 37.8 Fetal ultrasound showing sagittal (a) and axial (b) images of the left kidney with upper- and lower-pole hydroureteronephrosis. (c) Transverse view of the fetal bladder showing a ureterocele (arrow). After the patient was born, imaging studies showed a left duplex kidney with an upper-pole obstructed ureter ending in a ureterocele and lower-pole reflux (imaging studies not shown).

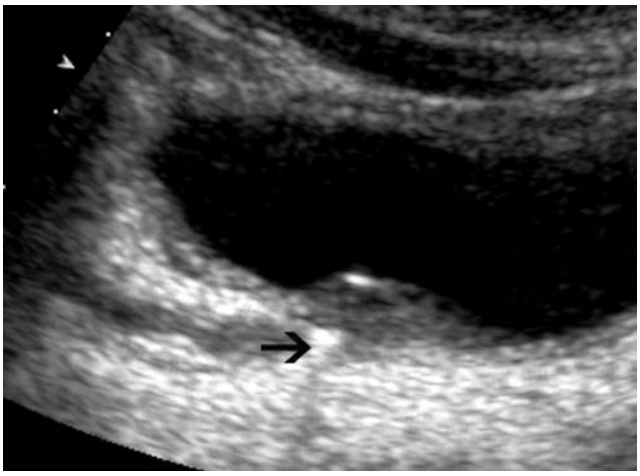


FIGURE 37.9 Distal ureteral stone. A sagittal ultrasound of the bladder demonstrates a small distal ureteral calculus (arrow) with mild hydroureter and edema at the UVJ.

better show the dysplastic upper pole and the degree of function, and may also show the site of ectopic ureteral insertion. With MRU, the benefit of nonionizing radiation study must be weighed against the potential need for sedation and higher cost (Figure 37.10).

Primary Megaureter versus Ectopic Ureter

IVP is no longer routinely performed in all cases of hydroureteronephrosis. A combination of ultrasound, MAG-3 renal scan, and MRU are useful in diagnosing and characterizing UVJ obstruction and distinguishing a primary

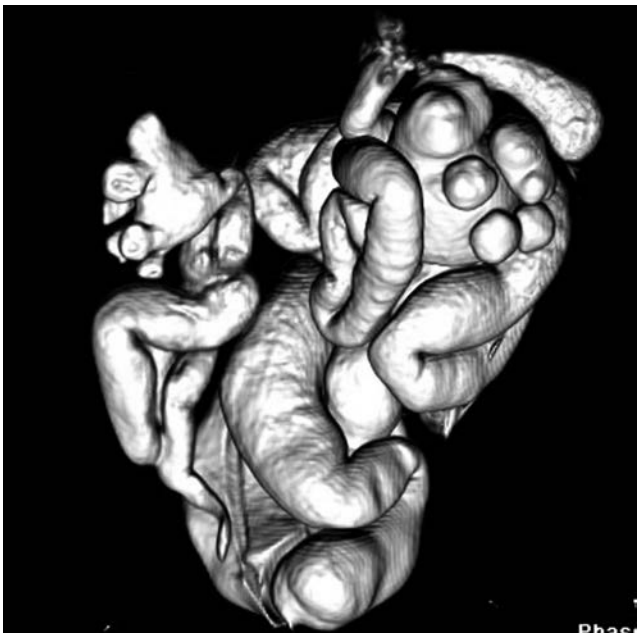


FIGURE 37.10 Magnetic resonance shaded rendering image of a urinary tract patient with prenatal hydronephrosis who was found to have severe bilateral hydroureteronephrosis postnatally. On the right, there is a UVJ obstruction of a bifid ureter. There is complete ureteral duplication on the left, with the upper-pole ureter inserting ectopically.

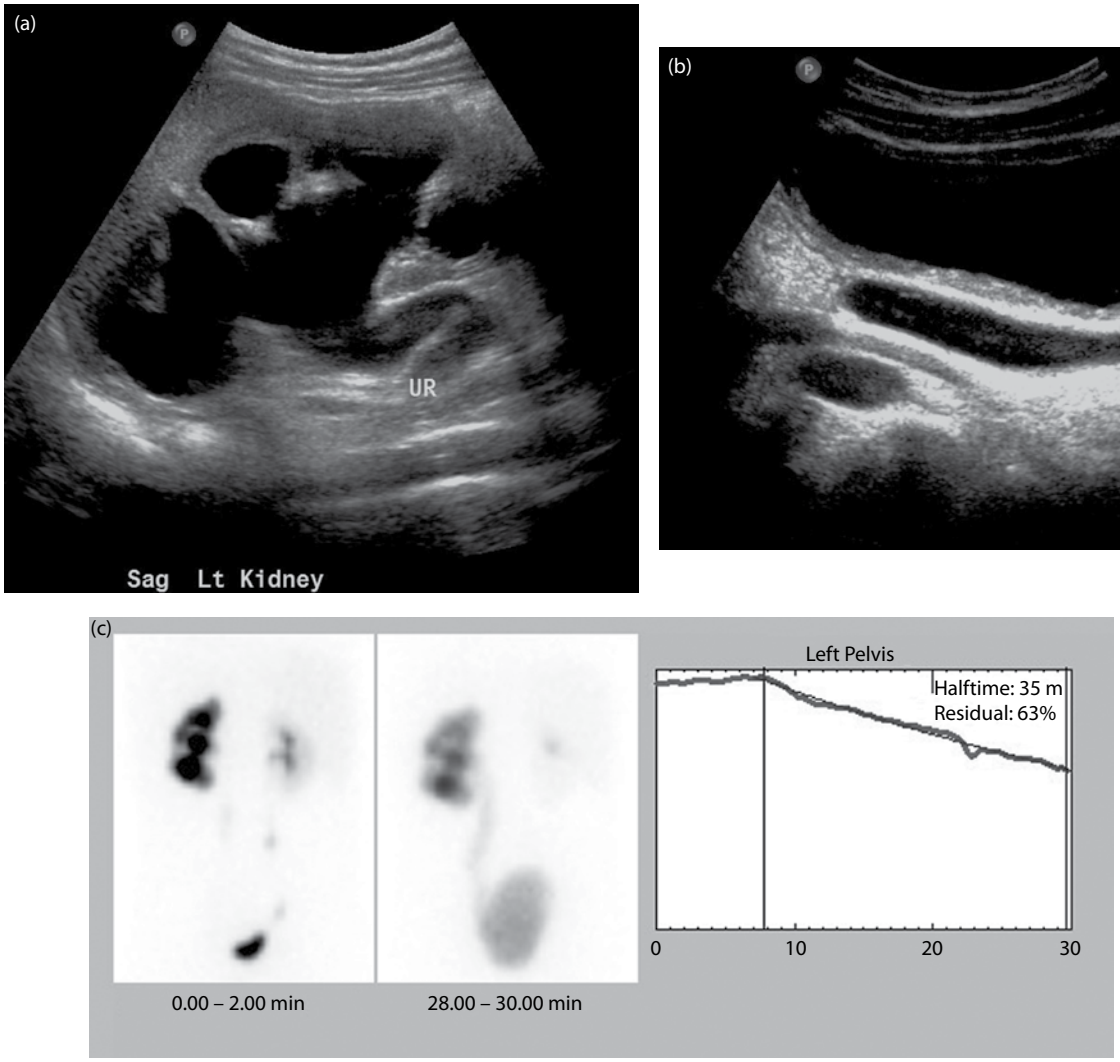


FIGURE 37.11 This patient, who presented with a febrile urinary tract infection, was found to have right primary megaureter. (a and b) The ultrasound images show left hydroureteronephrosis. (c) Obstruction was confirmed with obstructive values on a lasix renogram.

obstructive megaureter from a single-system ectopic ureter. This distinction is important, as a primary megaureter may be managed initially by observation, while an ectopic ureter usually requires surgical correction (Figure 37.11a–c).

Postoperative Assessment

For many patients who undergo repair of a UPJ or UVJ obstruction, the dilatation of the renal collecting system and ureter typically does not resolve during the first few months after surgery. In this setting, a nuclear medicine renogram or intravenous pyelogram may be invaluable in demonstrating that the obstruction has been corrected despite continued dilatation of the collecting system. Alternatively, if there is concern for postoperative collecting system obstruction, IVP is an excellent study for assessing the anastomosis site.

Another setting in which IVP may be valuable is in looking for an anterior crossing vessel that may produce intermittent renal colic due to intermittent kinking at the UPJ. Such a vessel may present as a proximal ureteral filling defect that disappears after surgically transposing the pelvis and ureter anterior to the crossing lower-pole artery (Figure 37.12).

Renogram

Introduction

Dynamic renal scintigraphy, or renogram, can be used to evaluate both renal cortical function and collecting system drainage.[52] Evaluation of the collecting system can be enhanced by adding a diuretic, such as furosemide, to perform a diuretic renogram. The preferred radiopharmaceutical is ^{99m}Tc-MAG-3, which is preferentially excreted by renal tubular secretion with a high extraction efficiency. The North American consensus guidelines[6] recommend an administered dose of ^{99m}Tc-MAG-3 of 3.7 MBq/kg (0.1 mCi/kg), with a minimum dose of 37 mBq (1.0 mCi) and a maximum dose of 148 MBq (4 mCi). A 1-minute flow study is typically performed at the start of the renogram in adults, but it necessitates a

FIGURE 37.12 This intravenous pyelogram of an 8-year-old boy who presented with flank pain shows the "hooked" appearance of the proximal ureter that is characteristic of high ureteral obstruction from a crossing vessel.

higher radiopharmaceutical dose and is rarely indicated in pediatric patients. A renogram also could be performed with ^{99m}Tc–diethylene triamine pentaacetic acid (DTPA), but DTPA produces studies with lower image quality due to its lower extraction fraction compared with MAG-3.[53] As it is excreted essentially by only glomerular filtration, DTPA does have a role in the quantitative determination of glomerular filtration rate (GFR).[54]

Patients should be well hydrated to maintain adequate renal blood flow to reliably assess renal cortical function. Many protocols recommend an intravenous saline infusion during the study to replete intravascular volume and produce a saline diuresis to ensure sufficient urine volume to evaluate collecting system function.[55] This can be particularly important when performing a diuretic-enhanced renogram. Urinary catheterization is recommended, particularly in younger children, who may not void on command, and in patients with bladder dysfunction. Retained urine, especially in a full bladder, may impede ureteral drainage, or rarely may reflux into a ureter. Either of these processes may produce a false-positive study.

Renogram images are acquired using a gamma camera.[55] Images are typically as a dynamic study for 20 minutes, during which time much of the ^{99m}Tc-MAG-3 has been cleared from the soft tissues of the body and excreted in the urine. Renal cortical function can be evaluated by quantitatively assessing cortical uptake of the tracer and transit of the tracer into the collecting system. Frequently, image analysis will demonstrate normal renal excretion and collecting system clearance, and the study can be terminated. Tracer excretion will be slowed with renal insufficiency, and visual inspection of images is required to determine if renal retention of the tracer reflects cortical dysfunction or collecting system obstruction. Sometimes, delayed planar images are helpful to demonstrate slow but continued drainage of the tracer from a dilated or partially obstructed collecting system, but a furosemide diuresis is usually preferred.

Diuresis can be induced by administration of furosemide at a dose of 1 mg/kg. The usual maximal dose is 40 mg, unless there is impaired renal function or if the patient has been on chronic diuretic therapy. There are at least three different approaches for performing a diuretic renogram, with different times for intravenous furosemide administration. Administration of furosemide at least 20 minutes (F + 20) after administration of the tracer was endorsed by a 1992 joint statement of the American Society of Fetal Urology and the Pediatric Council of the Society of Nuclear Medicine.[56] Diuretic can also be administered some period of time (F – 15) before administration of the tracer.[57] Finally, some clinicians, particularly in North America and Australia, favor administering the tracer and diuretic at the same time (F – 0).[58] Each method requires a different approach to image acquisition, analysis, and interpretation. F – 15 and F – 0 have the potential advantage of being shorter in duration, but F + 20 usually has the benefit of allowing collecting system drainage to be assessed in the absence of substantial tracer accumulation in the renal cortex. The F + 20 approach may allow furosemide administration to be avoided in patients shown to have normal spontaneous collecting system drainage. The F + 20 approach may also be useful in identifying a dilated, nonobstructive collecting system after surgical correction of an obstruction. If the dynamic renogram demonstrates significant cortical dysfunction, a diuresis phase may not be indicated to evaluate the collecting system, and moreover, there may be an impaired response to a diuretic.

Hydronephrosis, Hydroureteronephrosis, and Obstruction

For the assessment of a hydronephrotic kidney or hydroureteronephrotic collecting system, the MAG- 3 renal scan provides quantitative information regarding renal function and drainage of the dilated system. Based on the results of the MAG-3 scan, one can determine whether relative renal function appears to have been compromised and whether drainage is in the normal, intermediate, or obstructive range (for clearance time of half the tracer [T1/2], <10–15 minutes is normal, 15–20 [or 10–20] minutes intermediate, and >20 minutes obstructive). This information is particularly crucial for the postnatal assessment of prenatal hydronephrosis in healthy, asymptomatic babies. Typically, one waits until 1 month of age prior to performing the MAG-3 scan in order to ensure adequate renal maturity. Then the severity of an apparent UPJ or UVJ obstruction can be accurately assessed. These functional results, in conjunction with postnatal ultrasound findings, should enable one to develop a rational management plan—rarely for immediate surgery, and usually for follow-up imaging with serial ultrasound or MAG-3 studies, depending on the initial findings (Figure 37.13a–e).

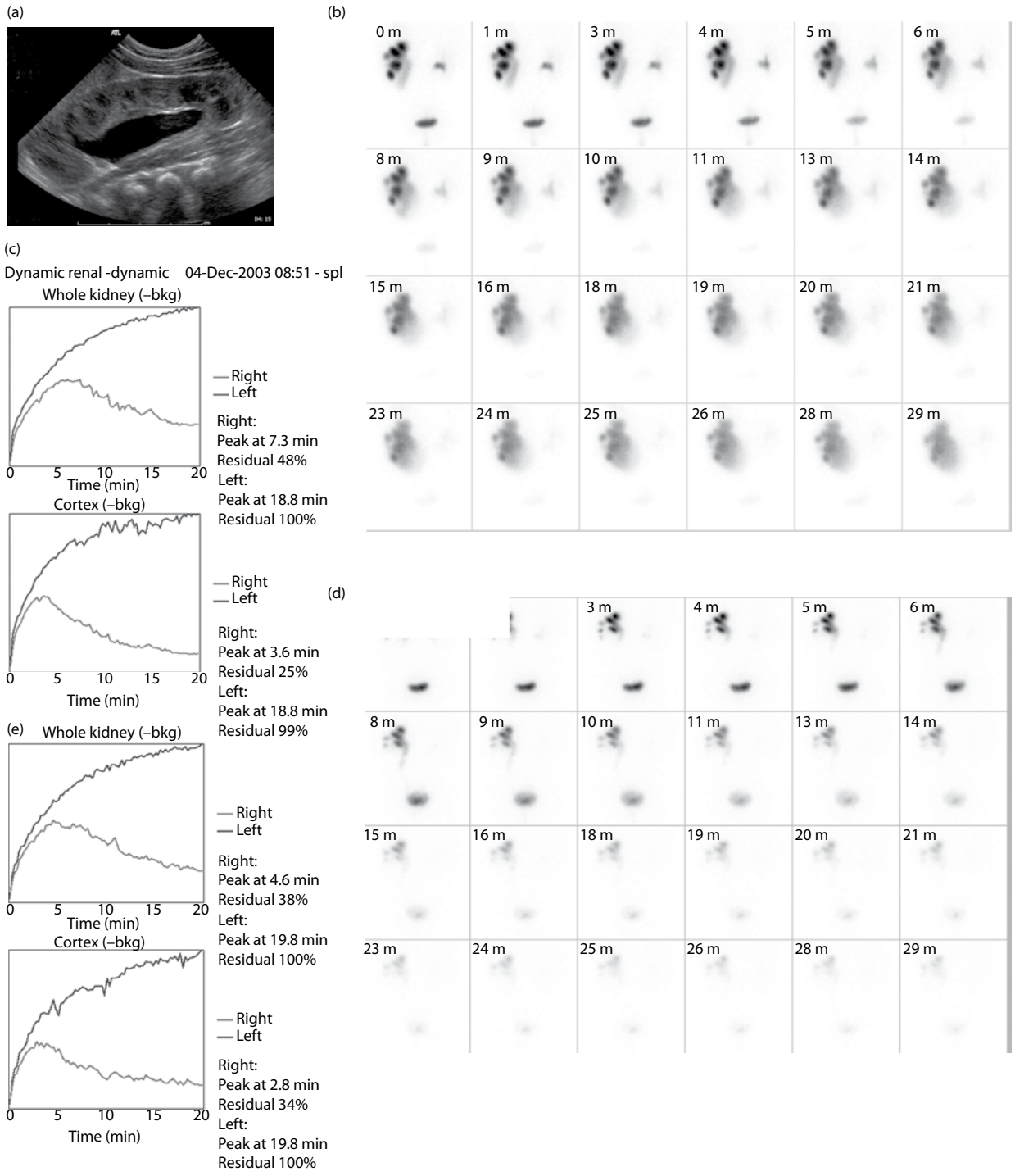


FIGURE 37.13 Two-month-old infant with prenatal hydronephrosis. (a) A postnatal ultrasound demonstrates unilateral moderate hydronephrosis. (b and c) An initial MAG-3 study with lasix demonstrates delayed drainage of the left kidney due to a UPJ obstruction. The time–activity curve demonstrates delayed excretion of contrast in the obstructive range. (d and e) A postoperative MAG-3 examination demonstrates improvement.

Computed Tomography or Computed Axial Tomography

Introduction

Computed tomography (CT), also known as computerized axial tomography (CAT), is a widely used modality for adult urinary tract imaging because of its applicability to stone disease, trauma, and the evaluation of renal masses, but it is used more sparingly in children due to the concern of radiation exposure.

Early CT scans acquired one "slice" or axial cross section of information at a time. With spiral or helical scanners, x-rays are emitted and detected as the patient

moves continuously through the scanner, creating a volume of information. Multislice or multidetector computed tomography (MDCT) scanners have multiple detectors rotating simultaneously around the patient with the effect of increasing spatial resolution and decreasing the time to perform a study over standard spiral scanners.

With a volume of information created, images can be reconstructed in many planes and reformatted to enhance the conspicuity of ureters. The ease and speed of obtaining large quantities of information by CT scan needs to be weighed against the radiation risk and financial cost of the examination. Depending on the method, the absorbed radiation dose of a single CT scan of the abdomen is significantly greater than that of an abdominal radiograph. The rapidly growing tissues of children are very susceptible to the deleterious effects of radiation.

Contrast and non-contrast-enhanced CT scans are used in the evaluation of the ureter. Non-contrast-enhanced CT is used for the evaluation of nephroureterolithiasis and resulting obstruction. Contrast-enhanced CT, especially timed during the excretory phase, is useful for showing the opacified ureters. Multiphase CT scans evaluate the genitourinary system without contrast, and then with contrast, timed to the cortical and excretory phases of contrast enhancement. Multiphase CT scan should be used sparingly in children due to the high radiation dose.

Methods used to enhance ureteral opacification after contrast administration include abdominal compression with bellows,[59] intravenous hydration during the examination,[60] prone and supine imaging,[61] multiplanar reformatting, and virtual endoscopy.[62] The angiographic phase of contrast enhancement is useful in clarifying vascular anatomy in the cases of trauma or UPJ obstruction.[63–65]

Nephroureterolithiasis

The spiral CT scan, without contrast, can rapidly assess the upper tract for a calculus. On the basis of Hounsfield units, it has the advantage, relative to ultrasound, of distinguishing a stone from an air bubble or intraluminal polyp. Its disadvantage is the ionizing radiation entailed; however, multiple low-dose methods have now reduced CT significantly.[66] However, ultrasound remains the initial imaging modality for suspicion of nephrolithiasis[67] (Figure 37.14).

Ureteral Trauma

In the assessment of urologic trauma, the CT scan with contrast is invaluable. Images performed during the excretory phase of contrast enhancement are the best for evaluation of the ureter.[68–70] CT is capable of demonstrating extravasation due to pelviureteric disruption of the ureteropelvic junction secondary to hyperextension injuries or ureteral disruption due to penetrating trauma. It also affords one the capability of assessing injuries to associated organs, such as the spleen or liver (Figure 37.15).

Other Ureteral Anomalies

CT has a wide range of uses, including the assessment of an abnormal course of the ureter, such as a retrocaval ureter,[71] ectopic ureteral insertion,[72] or ureteral obstruction.

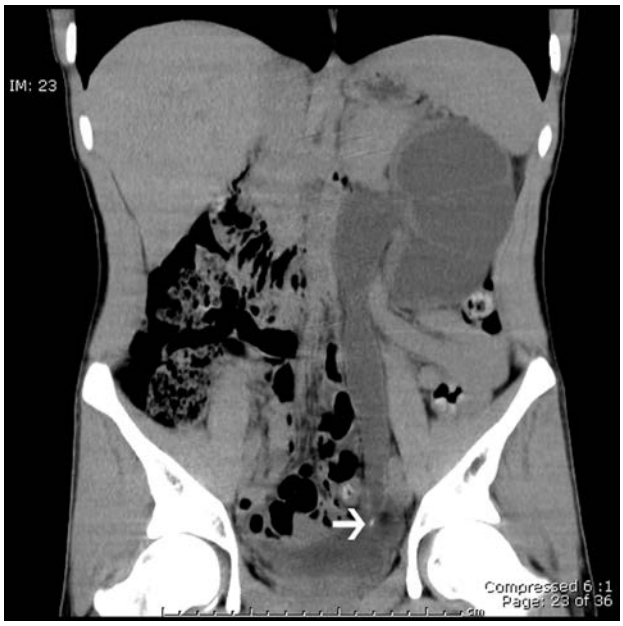


FIGURE 37.14 CT with coronal reformatting showing a left UVJ calculus (arrow) in a patient with primary megaureter.

FIGURE 37.15 Am axial CT image performed during the excretory phase of contrast enhancement demonstrates right perinephric contrast extravasation due to a ureteral tear at the UPJ.

The CT scan with contrast is also valuable in assessing the solid retroperitoneal mass, such as Wilms' tumor or neuroblastoma, and its effect on ureteral anatomy.

Specialized Opacification Techniques

Introduction

The specialized opacification techniques enable one to visualize the ureter precisely in complex anatomical or operative clinical settings.

Retrograde Ureterography and Pyelography

Retrograde ureterography and pyelography are performed cystoscopically in the anesthetized child through

a ureteral catheter using one-half strength Cystografin. It is used to opacify the distal ureter prior to pyeloplasty, to ensure normal distal ureteral anatomy, and to confirm the level of ureteral obstruction. It can be invaluable in distinguishing a typical UPJ obstruction from rare lesions, such as fibroepithelial polyps of the UPJ and midureteral strictures. Retrograde pelography is also useful in the assessment of ureteral trauma and evaluation of the stone patient prior to ureteral stone basketing or lithotripsy. In difficult diagnostic situations, such as unusual duplication anomalies or ectopic ureters, retrograde ureterography and pyelography can be extremely valuable in defining the anatomy (Figure 37.16a and b).

Antegrade Pyelography and Ureterography

Antegrade pyelography and ureterography are uncommon studies, utilized to define unusual anatomy, often in conjunction with the goal of draining a hydronephrotic collecting system. The antegrade study can be extremely valuable in defining postsurgical complications, such as obstruction or urinary extravasation. It is particularly useful in defining the anatomy of duplex collecting systems, dilated ureters draining ectopically, and collecting systems associated with poorly functioning kidneys that do not excrete contrast well.

Whitaker Test

The Whitaker test is a physiologic study combined with the anatomic benefit of antegrade pyelography, used to assess upper tract obstruction. The Whitaker test is performed with percutaneous access to the kidney and catheter drainage of the bladder. Pressures within the renal pelvis and bladder are measured during a constant infusion of contrast into the renal pelvis. Pressure differentials between the kidney and bladder of less than 15 cm of water are considered normal, whereas pressure differentials that exceed 20 cm of water are consistent with obstruction. During the course of the study, imaging of the ureter clearly demonstrates the level of obstruction. This test is particularly valuable in assessing a postoperative result when hydronephrosis persists and renal function is so impaired that nuclear renography is nondiagnostic.

Magnetic Resonance Urography

MRU offers the combination of high-resolution anatomic imaging and functional information of the genitourinary system without radiation. In children, MRU is used to evaluate urinary tract dilatation and differentiate it from obstruction,[73–75] evaluate complex genitourinary anatomy,[76] and assess the ureters.[77]

MRU provides beautiful assessment of renal anatomy and can provide functional imaging comparable to that of renal diuretic scintigraphy.[74,78] Unlike IVP and scintigraphy, visualization of the ureters and kidneys is not dependent on renal function. MRU is especially useful in children with obstruction or complex anatomy. Some advocate this method to replace ultrasound and renal diuretic scintigraphy in the evaluation of hydronephrosis.[74]

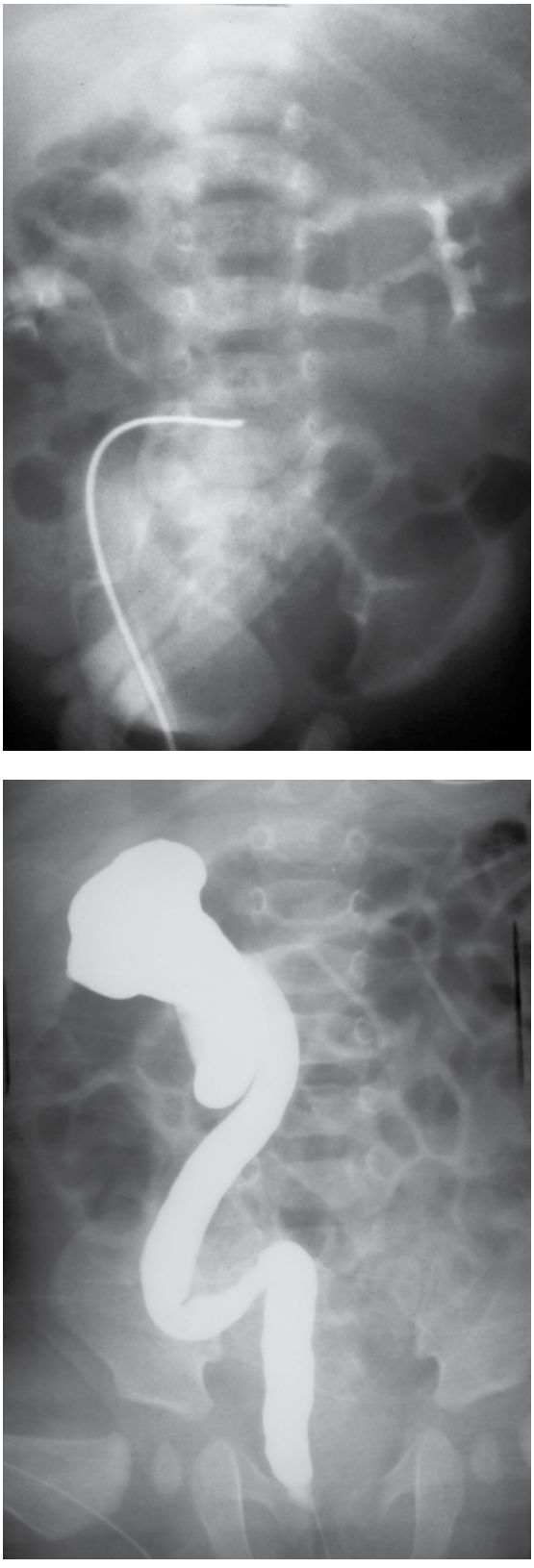


FIGURE 37.16 Intravenous pyelogram and retrograde ureterogram in a patient with a right upper-pole ectopic ureter. (a) IVP in a newborn infant demonstrates lateral deviation of the right lower-pole collecting system. The left kidney appears normal. (b) A retrograde ureterogram demonstrates the ectopic upper-pole ureter and pelvis.

Many protocols are widely available.[73,74,79,80] Modern magnetic resonance techniques and improved coils allow for improved spatial and temporal resolution and faster acquisition time. The anatomy of the genitourinary system can be most easily surveyed using fluid-sensitive sequences, which give good tissue contrast between the fluid-containing collecting system and renal parenchyma and other organs. Functional information can be obtained using fast imaging magnetic resonance techniques after contrast administration and allow evaluation of parenchymal perfusion, the GFR,[81] the renal excretory function, and urinary drainage.[82] However, patients who receive contrast administration of gadolinium-based contrast agents and have severely impaired renal function are at risk for nephrogenic systemic fibrosis (NSF), a rare systemic fibrosing ailment that mainly involves the skin. Thus, patients with acute or chronic renal failure and a low GFR (<45 mL/min/1.73 m^2), or acute renal insufficiency of any severity due to the hepatorenal syndrome or in the perioperative liver transplantation period,[83] should not have contrast administration.

In order to obtain good-quality images, children must lay supine with minimal motion within the bore of the MRI, which is a relatively narrow tunnel. Since even the simplest examinations for the evaluation of genitourinary anatomy requires at least half an hour, those who are unable to hold still for this period of time require sedation. For longer studies that provide functional information, children need an IV for intravenous contrast, furosemide, and hydration. Due to the large volume of urine that is produced after hydration and diuretic use, Foley catheter drainage of the bladder is helpful for patient comfort and to reduce the likelihood of the patient waking up during sedation. Like other studies, patient and family preparation is crucial. Guidance from child life specialists and skilled technologists and use of videos and music often reduce the need for sedation (Figure 37.17).

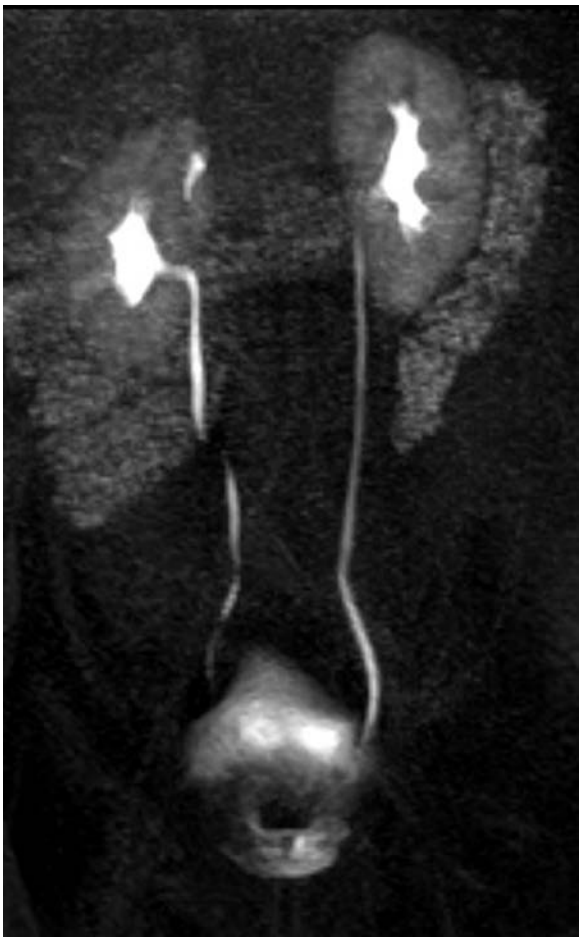


FIGURE 37.17 This MRU shows a right duplex kidney with the right dysplastic upper pole the cause of the girl's day and night incontinence.

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CHAPTER
38

Ureteral Anomalies and Their Surgical Management

Kathleen Kieran and Christopher S. Cooper

INTRODUCTION

Although ureteropelvic junction obstruction, ureteroceles, and obstructive megaureters account for the vast majority of ureteral obstructions, the pediatric urologist must consider less common causes of ureteral obstruction when evaluating a patient with complaints that suggest ureteral pathology. While the aforementioned common causes of ureteral obstruction are addressed elsewhere in this book, this chapter describes the pathophysiology, evaluation, and management of ureteral obstruction secondary to retrocaval ureter, ureteral valves, ureteral strictures, and ureteral polyps. Anomalies of ureteral number are also briefly discussed, although the reader is directed to the pertinent chapter (Chapter 40) for a more detailed discussion on the surgical management of ureteral duplication anomalies and ectopia.

EMBRYOLOGY

Evaluation of the patient with a suspected ureteral anomaly should be conducted in the context of an understanding of normal ureteral development. The mesonephros develops at 24–26 days and progresses caudally along the longitudinal axis of the embryo, giving rise to the mesonephric (Wolffian) ducts and tubules. The Wolffian ducts ultimately give rise to the ureteral bud, which grows cranially in the fourth week of gestation; upon contact with the metanephric mesenchyme, reciprocal coinduction results in the development of the definitive fetal kidney.[1,2] Abnormalities in the growth or development of the Wolffian bud, or in the reciprocal coinductive pathways, may result in abnormal ureteral structure and function. Additionally, the clinician must remember that nearby structures are also forming as the ureter develops, and abnormalities in these structures may affect ureteral development.

PATIENT PRESENTATION AND EVALUATION

The ureteral anomalies to be discussed all have compromise of the ureteral lumen by either intrinsic or extrinsic factors. Thus, patients typically present with symptoms of ureteral obstruction, such as flank, abdominal, or back pain; hematuria; urinary tract infection (UTI); and nausea and/or vomiting. With the increasing employment of cross-sectional imaging, these ureteral anomalies may be found incidentally; however, on further questioning, many of these patients may recall symptoms similar to those described.

The need for and choice of laboratory and radiographic studies is dictated by the clinician's suspicion for a ureteral etiology for the presenting symptoms. At the very least, a urinalysis should be performed to exclude infection; a chemistry panel, as well as a complete blood count, may also prove useful in patients with suspected infection or severe obstruction. Renal ultrasonography is typically employed as the initial imaging study, since it allows assessment of the degree of pelvic, calyceal, and ureteral dilatation, as well as parenchymal echogenicity. If the initial renal sonogram suggests a ureteral anomaly, further evaluation is typically undertaken with either cross-sectional imaging (computed tomography [CT] scan or magnetic resonance imaging [MRI]) or cystoscopic evaluation with retrograde pyelogram in order to better define the laterality and extent of any pathology.

RETROCAVAL URETER

The reported incidence of retrocaval ureter is about 1 in 1000 and occurs two to three times more frequently in males.[3] Patients with retrocaval ureter may also have cardiovascular or genitourinary anomalies.[4,5] The retrocaval ureter almost always involves the right ureter; however, rare cases involving the left side have been reported, usually associated with situs inversus.[6,7] Despite its name, the retrocaval ureter arises secondary to anomalous vascular development. In the fetus, the supracardinal vein lies dorsal to the ureter and usually forms most of the infrarenal segment of the inferior vena cava. The subcardinal, or posterior cardinal, vein lies ventral to the ureter; if the subcardinal vein persists, it becomes the infrarenal segment of the vena cava. When the inferior vena cava is derived from the subcardinal vein, the ureter encircles the vena cava, with a portion of the ureter running behind

the vena cava.[8] While most patients with a retrocaval ureter are asymptomatic, others may present with pain, hematuria, UTIs, or stones in the setting of functional or anatomic ureteral obstruction;[9,10] the retrocaval segment of the ureter is often stenotic. In children diagnosed with retrocaval ureter, UTI is often the presenting symptom.

Based on radiographic criteria, two types of retrocaval ureters have been described.[11] Type I (low-loop) retrocaval ureter is more common and is associated with moderate or severe hydronephrosis, with significant medial deviation of the ureter at the L3 vertebral body. Type I retrocaval ureters typically have an S-shaped or fishhook deformity (Figure 38.1). Type II (high-loop) retrocaval ureter is seen less frequently; it is associated with less pronounced hydronephrosis and less medial deviation. Type II retrocaval ureters have a "sickle"-shaped appearance at the point of medial deviation. While widespread use of ultrasonography has resulted in more cases of retrocaval ureter being diagnosed following identification of hydronephrosis, the clinician must be careful to exclude other causes of retroperitoneal pathology. Both CT and MRI are sensitive and have specific modalities for confirming the diagnosis;[4,12,13] the latter has the benefit of avoiding radiation exposure. Nuclear medicine renal scans may be helpful to estimate relative renal function and identify the degree of obstruction.

Surgical treatment involves division of the ureter, enabling ureteral continuity to be reestablished anterior to the inferior vena cava. When the proximal ureter is redundant or stenotic, excision of a portion of the ureter may be necessary. Both open and laparoscopic or robotic approaches have been successfully employed for repair (Figure 38.2).[13–17]

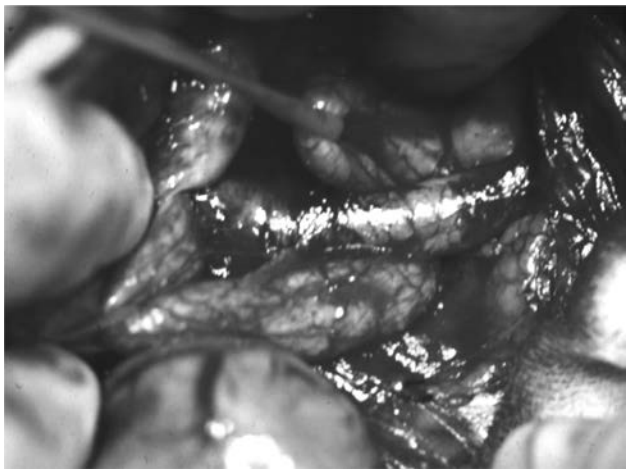

FIGURE 38.2 Retrocaval ureter.

URETERAL STRICTURE

Ureteral stenosis or strictures are most commonly seen in the distal ureter and can be associated with megaureters; however, midureteral lesions may also occur (Figure 38.3).

FIGURE 38.1 Intravenous pyelogram of a patient with a retrocaval ureter. Note the extensive dilatation of the proximal ureter and medial deviation at the third lumbar vertebra.

FIGURE 38.3 Retrograde ureteropyelogram demonstrating short ureteral stenosis.

Congenital strictures tend to occur in locations where the ureter is closely associated with another structure (including the kidney or bladder), but the exact precipitating events leading to stricture development are unknown. Abnormalities of the contralateral renal unit have also been reported in conjunction with congenital midureteral strictures.[18] Although the strictured ureter is uniformly lined by transitional epithelium, other histologic findings are variable and may range from hypertrophied smooth muscle to a near absence of muscular fibers.[19,20] Like other ureteral lesions, the symptoms of congenital ureteral strictures are variable and depend on the degree of obstruction and renal function, and the pathologic changes proximal to the stricture vary, reflecting the severity and duration of the obstruction. Pyelonephritis, complicating obstruction, may lead to decreased renal function.[21]

Ureteral strictures may be discovered incidentally during an evaluation for antenatal hydronephrosis. Although these congenital strictures can be asymptomatic, they may be less amenable to conservative management than other causes of antenatal hydronephrosis.[19] Because obstruction at any location within the collecting system may present with similar symptoms and radiographic findings, the clinician must be careful to identify the precise location of the affected area prior to proceeding with surgical repair. Confirmation of the presence and length of the ureteral stricture is best accomplished by retrograde ureteropyelogram.[22] Endoscopic evaluation also permits consideration of endoscopic treatment. Both dilatation and incision have been successfully employed for ureteral strictures, but the initial success rates and long-term durability of these procedures are lower than for open repair. Open techniques typically involve excision of the affected segment with reestablishment of ureteral continuity.[21] Laparoscopic and robotic modalities have also been used successfully.[23]

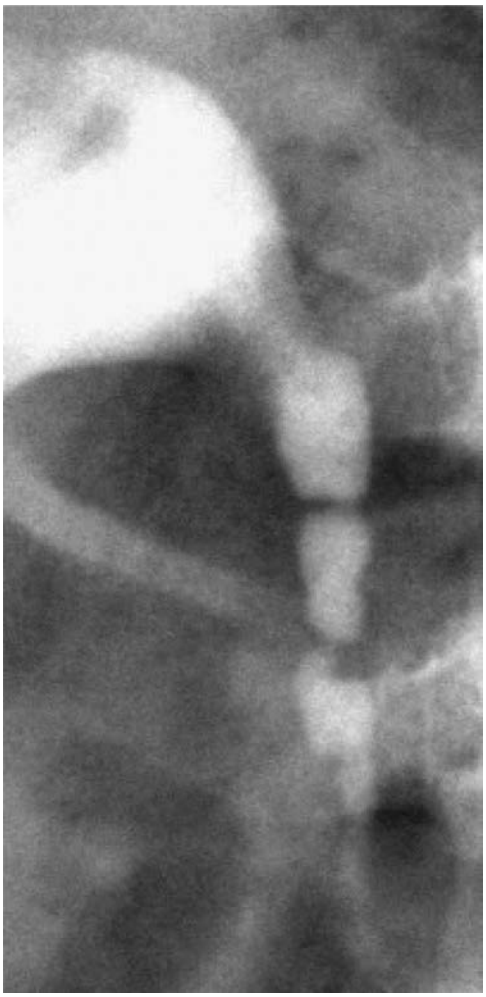

FIGURE 38.4 Intravenous pyelogram demonstrating nonobstructive Ostling's folds in the proximal ureter of a 5-month-old infant.

URETERAL VALVES

Ureteral valves are an uncommon finding, with fewer than 100 cases reported in the literature. Valves are frequently associated with other ureteral anomalies, including duplication, ectopia, and vesicoureteral reflux.[24] Ureteral valves and coexisting ureteral strictures have also been reported.[25] Ureteral valves are more common in boys and on the left side (although more recent publications dispute these findings).[26] Histologically, valves are transverse folds of tissue consisting of smooth muscle extending into and blocking the ureteral lumen, covered by normal transitional epithelium.[20] These valves are believed to represent abnormal persistence of transverse folds that arise as part of normal ureteral development (Ostling's folds; see Figure 38.4).[21] Two types of ureteral valves have been described:[27] one with ureteral stenosis at or distal to the site of the valve, and one that involves a distal ureter of normal caliber. Both types of valves have the orifice and long axis of the distal ureter eccentrically located with respect to the long axis and lumen of the proximal dilated ureter (Figure 38.5). This configuration selectively inhibits antegrade but not retrograde flow.

Patients with ureteral valves typically present with flank pain and hydronephrosis. Treatment of the valves depends on the location and typically involves resection and reconstruction with ureteropyelostomy, ureteroureterostomy, or ureteroneocystostomy.

URETERAL POLYPS

Fibroepithelial polyps of the ureter are the most common benign neoplasm of the ureter;[28] the exact etiology is unknown, and it is believed that some polyps are congenital, while others arise secondary to factors such as inflammation. Histologically, the polyps have a fibrous core covered by normal transitional cell epithelium.[29] Bilateral polyps have been reported, as have polyps in conjunction with upper tract neoplasia.[30] Polyps are more common in adults than children, and in males than females.[31] Symptomatic polyps typically present with flank pain or hematuria, and contrast-enhanced ureteral imaging (intravenous pyelogram or CT) will show a filling defect that is either vermiform or corkscrew in appearance (Figure 38.6).[31,32] Demonstration of contrast enhancement or Doppler waveform within the mass will differentiate polyps from fungal balls, sloughed papillae, and clots.

FIGURE 38.5 Schematic configuration of a ureteral valve; at the level of the valve, the ureteral lumen is eccentric. The proximal ureter is dilated and the distal ureter is decompressed.

FIGURE 38.6 Retrograde ureteropyelogram demonstrating a long, smooth filling defect in the distal ureter, consistent with fibroepithelial polyp.

Resection of the polyp can be accomplished either endoscopically or through surgical excision. Endoscopic management may be performed either antegrade or retrograde, but care should be employed to ensure that the entire base is resected, as recurrent growth may be noted if any polyp tissue remains. Open or laparoscopic polyp excision with ureteroureterostomy may also be employed.[28,31,33]

ANOMALIES OF URETERAL NUMBER

Ureteral duplication is discussed in detail elsewhere in this text.

Ureteral triplication (Figure 38.7) is exceedingly rare, and most publications are case reports or small case series. Triplication arises either from an additional ureteral bud from the mesonephric duct or from division of the existing ureteral bud into three parts. Four types of ureteral triplication have been described.[34] Type I (35%) is complete triplication, Type II (21%) is incomplete triplication, Type III (31%) is a trifid ureter, and Type IV (9%) occurs when one of a set of double ureters is bifurcated. Triplication occurs more frequently in girls than boys and on the left versus the right side. It is associated with coexisting unilateral or contralateral ureteral anomalies, such as contralateral duplication (37%), ureteral ectopia (28%), renal

FIGURE 38.7 Voiding cystourethrogram showing complete (Type I) right ureteral triplication. (Reprinted from *J Ped Urol*, 7, Kokabi N et al., Ureteral triplication: A rare anomaly with a variety of presentations, 484–7, Copyright 2011, with permission from Elsevier.)

dysplasia (8%), ureterocele, vesicoureteral reflux, and contralateral triplication.[35–37] It has also been reported in conjunction with syndromes such as VACTERL.[38] Although many cases of ureteral triplication are likely asymptomatic, patients may present with symptoms of UTI, flank pain, incontinence, or obstruction, similar to patients with duplication anomalies.[38–40] Imaging studies, such as sonography, voiding cystourethrography, nuclear medicine scans, and tomography, should be selected based on patient symptoms; diagnosis of ureteral triplication requires a high index of clinical suspicion. Management of ureteral triplication should be tailored to the individual patient and directed by symptoms. In incidental cases, no therapy may be needed, while patients with ureteral ectopia, ureteroceles, or vesicoureteral reflux may benefit from lower urinary tract reconstruction, and patients with poorly functioning renal moieties may benefit from partial nephrectomy.

Ureteral quadruplication has been reported in only a few cases.[41] Again, a high index of suspicion is necessary for the diagnosis, and imaging studies and definitive therapy should be guided by the patient's presenting complaints.

SURGICAL TECHNIQUE

Ureteral obstruction often requires operative intervention. Both laparoscopic and open approaches have been employed with equivalent success rates; hospital stays may be shorter and pain medicine requirements minimized with the laparoscopic approach. Regardless of the surgical modality selected by the surgeon, careful attention should be paid to basic surgical principles.

The blood supply of the ureter is derived from nearby structures, with anastomosing vessels allowing mobilization and division of portions of the ureter. Proximally, the ureteral blood supply is derived from branches of the renal and gonadal arteries, while the pelvic portion of the ureter derives its blood supply from the vesical and middle rectal arteries and, in some cases, from the internal and common iliac arteries. Anastomosing blood vessels, as well as nerve fibers, run in the adventitia, before penetrating the muscle layers and forming a submucosal plexus.[42] Thus, rough handling of the ureter may damage any of these layers with resulting compromise of the ureteral blood supply. Gentle handing, aided by ureteral traction sutures, will in many cases avoid iatrogenic ureteral injury and subsequent stricture.

The majority of ureteral anomalies discussed in this chapter are best managed by ureteral division with or without excision of the affected segment, followed by primary reanastomosis. Surgical wound healing is optimized by a tension-free closure, which may require mobilization of the proximal and/or distal ureter, the bladder, and/or the kidney. Spatulation of the ureter prior to reanastomosis will help prevent iatrogenic stricture secondary to wound contracture; spatulation of the stenosed segment with incorporation of this area into the repair may also be considered if there is concern for adequate ureteral length. Absorbable sutures should be employed for the anastomosis, with the knot tied outside the lumen, in order to minimize exposure to urine and ensuing local tissue reaction. Because urine extravasation may result in a local inflammatory reaction with subsequent fibrosis,[43] either ureteral stents or external drains are typically employed to minimize the sequelae of extravasation. Ureteral stents promote urinary flow through the ureter and diminish extravasation of urine. Nonsuction drains placed near the anastomosis permit evacuation of any extravasated urine from the site of repair.

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CHAPTER
39

Megaureter

David B. Joseph

INTRODUCTION

In 1923, J. R. Caulk described a patient with distal ureteral dilatation without evidence of hydronephrosis and coined the term *megaloureter*.[1] The word *megaureter* conveys the image of a grossly dilated ureter. The term is nonspecific and does not provide insight into the pathophysiology. In 1958, D. Innes Williams described the term *megaureter* as "a chronic dilatation of the ureter for which no organic obstructive cause can be found: it implies an ignorance of the fundamental pathology and it is hoped that it will be replaced in time by a more enlightened nomenclature." He also excluded the term in conditions such as those secondary to ureterocele, congenital stricture, urethral obstruction, ectopic ureteral insertion, and urinary retention. Swenson, in 1955, postulated a neurologic etiology and, in order to provide peristalsis, treated such patients with urinary diversion, ureteral substitution, and ileal augmentation.[2] Knowledge of the megaureter has changed greatly over the past 15 years. In the past 15 years, and with the advancement in fetal sonography, we better understand the natural history of the megaureter and have gained better insight into treatment, but we still have a rather poor understanding of its pathophysiology (Figure 39.1).

HISTORIC PERSPECTIVE

Classification

Megaureter is synonymous with a dilated ureter, megaloureter, wide ureter, big ureter, and hydroureter—all descriptive terms that lack true meaning.[3] Cussen, in 1971, reported on autopsy findings of the urinary system in infants and children. He found that a child's ureter consistently measured less than 5 mm.[4] This was supported by the work of Hellstrom and coworkers, who reviewed excretory urograms in 100 boys and 94 girls. They directly measured ureteral size from imaging studies and uniformly found the ureter to be less than 6 mm.[5] By definition, a megaureter equates to a ureter of >8 mm in diameter. In 1977, Smith et al.[6] reported on a classification system developed by a working party of pediatric urologists.[7] The group presented their findings and recommendations at an international pediatric urologic seminar in Philadelphia in 1976. An agreement was made to standardize the nomenclature and classification of the megaureter. The megaureter was classified as primary, referring to a lesion intrinsic to the ureter, and secondary, denoting a reaction of the ureter to a process elsewhere. They went on to create the ABC subclassification: A, representing a refluxing ureter; B, obstructed; and C, not refluxing and unobstructed. King modified this classification in 1980, adding a fourth subclassification consisting of the refluxing, obstructed megaureter.[8] King's classification is used most often when describing the megaureter (Figure 39.2).

ANATOMY

In order to understand pathophysiology, it is important to have a framework of normal anatomy. The ureter is divided into three distinct regions: (1) the ureteropelvic junction, (2) the middle spindle, and (3) the ureterovesical junction. The ureterovesical junction is subsequently divided into the juxtavesicoureter and terminal ureter. The terminal ureter then separates into intramural and submucosal segments.[9]

The ureter is enclosed in a loose, ill-defined sheath within the retroperitoneum. This sheath forms a protective barrier for the adventitia, particularly when confronted with a neoplastic or inflammatory retroperitoneal process. Proximally, the ureteral sheath and the ureteral adventitia become continuous with the renal pelvis. Distally, the sheath and ureteral adventitia join to form Waldeyer's sheath, which extends into the bladder wall as a portion of the deep trigone.[9]

The ureter consists of three layers: adventitia, muscularis, and mucosa. The adventitia is composed of longitudinally running collagen[10] loosely attached to the underlying muscularis, allowing for unrestricted peristaltic activity. The muscularis is made up of smooth muscle cells interspersed with collagen. The inner muscle bundles are arranged longitudinally; the middle, circumferentially; and the outer, longitudinally.[11] This configuration changes into longitudinally oriented muscle fibers in each layer with sparse collagen as the ureter enters the bladder and intramural portion.[12,13] The mucosa consists of multiple layers of transitional epithelium lying adjacent to the lamina propria.

The ureter is supplied by a rich anastomotic arterial network. The proximal ureter is vascularized predominantly

FIGURE 39.1 Obstructed, refluxing megaureter with an unusually long obstructing distal ureterovesical segment. (Adapted from Joseph DB, Ureterovesical junction anomalies—megaureters. In. Gearhart JP, Rink RC, Mouriquand PDE eds., *Pediatric Urology*, WB Saunders: Philadelphia, 2000, p. 347.)

by an artery originating from the renal artery. The middle spindle receives a branch from the aorta and gonadal artery. The distal ureter is supported by arteries from the internal iliac, superior, and inferior vesical arteries.[14] A periureteral arterial plexus courses the full extent of the ureter through the adventitia.

The proximal ureter receives neuronal input via the renal and aortic plexus. Unmyelinated nerves travel throughout the adventitial layer.[10] The middle spindle is innervated by the superior hypogastric plexus, and the ureterovesical segment by the pelvic plexus.[15] Both adrenergic and cholinergic nerves have been identified within the ureter.[16] It is interesting that ureteral peristalsis is modulated by, but not dependent on, neuronal input.

PATHOPHYSIOLOGY

Obstructed Megaureter

The primary obstructed megaureter has generated the most interest and investigation. It has been reported in approximately 25% of children with obstructive uropathy.[17–20] It is bilateral in 25% and four times more common in boys.[18,21] The left ureter is more frequently affected, and in 10%–15% of cases, the contralateral kidney may be dysplastic or obstructed.[3,21] Endoscopically, the obstructed ureteral orifice can have a normal appearance and insert appropriately on the trigone. Caulk and Swenson et al.[1,22] proposed that the obstructed megaureter was similar to the megacolon seen in Hirschsprung's disease. This, however, has been refuted based on histologic evidence showing ganglia present in the distal primarily obstructed megaureter in a distribution similar to that of a normal ureter.[23]

Several different histologic abnormalities have been associated with the primary obstructed megaureter, indicating a spectrum of pathologic events. A localized deficiency of muscle fibers within the ureterovesical ureter with hypertrophy of circular muscle bundles immediately proximal to the deficiency has been described as an adynamic distal segment resulting in obstruction (Figure 39.3).[24–26] The degree of obstruction may be correlated with the percentage of circular fibers. Gregoir and Debled found three histologic variants of obstructed

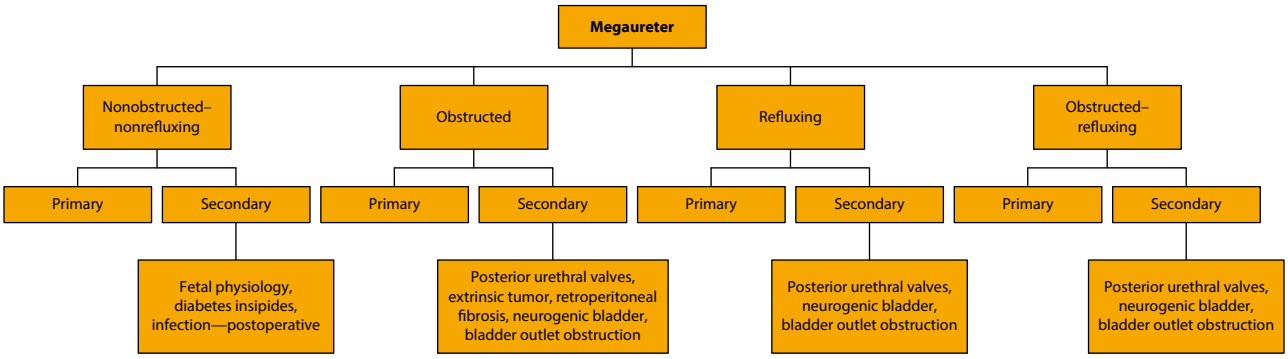

FIGURE 39.2 Classification of the megaureter. (Adapted from King LR. *J Urol* 1980;123(2):222–3.)

FIGURE 39.3 Obstruction due to an adynamic distal segment. (Adapted from Joseph DB, Ureterovesical junction anomalies—megaureters. In. Gearhart JP, Rink RC, Mouriquand PDE eds., *Pediatric Urology*, WB Saunders: Philadelphia, 2000, p. 355.)

megaureters: dense collagen infiltration of the terminal ureter, distal circular muscular hypertrophy, and varying degrees of distal muscular dysplasia.[27]

An increase in collagen deposition between the lamina propria and muscle bundles of the distal ureter has been seen with electron microscopy.[28–30] These pathologic changes result in muscular derangement and increased interstitial connective tissue within the ureterovesical junction. The middle spindle and ureteropelvic junction segments are spared.[31] Vlad et al. have found histologic qualitative and quantitative anomalies of connective, muscular, and nervous tissue, all of which are consistent with incomplete ureteral development and may compromise peristaltic activity.[32]

Dixon and associates assessed the histologic structure of the ectopic obstructed ureter and found that the terminal ureter was encircled by an additional thick collar of smooth muscle.[33] Normally oriented muscle layers were also present but had a diminished diameter. They speculate this embryologic malformation does not spontaneously resolve and becomes the subgroup of obstructed megaureter that requires early intervention.

Others have suggested abnormal acetylcholinesterase activity in the juxtavesical segment, a tonic response to noradrenaline, and increased intracellular calcium as etiologies of the obstructed megaureter.[34,35]

Some forms of the megaureter indeed improve with time.[17,18,36–40] Spontaneous improvement may be due to segmental maturation of the obstructed distal ureter. Nicotina and associates postulate segmental hypoplasia of the inner longitudinal muscle layer and the possible pathogenic involvement of transforming growth factor β (TGF-β), which has been shown to effect maturation of smooth muscle cells.[36] TGF-β delays muscle cell differentiation and is detectable in the 11- to 21-week-old fetus but diminishes thereafter. TGF-β has been found in the distal ureters of children who are less than 2 years of age with obstructive uropathy, but not in children older than 2 years of age who had repair of a nonobstructed megaureter.[36] The spontaneous improvement in the obstructed megaureter may correlate with TGF-β depletion within the first 2 years of life.[36]

Refluxing Megaureter

The refluxing megaureter is endoscopically characterized by a gaping lateral ureteral orifice. Bladder filling and cyclic voiding can transmit pressure into the ureter, resulting in mechanical enlargement (Figure 39.4). Lee and associates have found a twofold increase in the ratio of collagen fibers to smooth muscle fibers in the refluxing megaureter compared with the obstructed megaureter and control ureter.[41,42] They defined collagen fiber types and have shown an increase in collagen types I and III for both obstructed and refluxing megaureters. However, the refluxing megaureter contained a significantly greater percentage of type III collagen than other megaureters. Type III collagen is less distensible, raising speculation that this intrinsic characteristic stiffens the ureter. This may play an important role in the failure rate after operative correction of refluxing megaureters compared with the success noted in other forms of megaureters.[41]

FIGURE 39.4 Vesicoureteral reflux in a male neonate with elevated voiding pressure.

The influence of interstitial cells of Cajal on the pathophysiology of the megaureter has been explored (described by over 100 years ago as primitive intestinal neurons with similar cells noted by Klemm in the urinary system in 1999.126,127 These cells are localized with in muscle layers and thought to contribute in the control of peristaltic activity.[127]). Interstitial cells of Cajal have been reported as sparse or absent in the longitudinal muscle layer.[43] There is preliminary evidence to show that in the refluxing megaureter, compared with the obstructed ureter, the percent of smooth muscle is lower, along with a lower number of apoptotic cells and a lower percent of interstitial cells of Cajal. These factors can affect ureteral peristalsis.[44]

The refluxing megaureter associated with prune belly syndrome represents a unique abnormality.[45] The gross appearance of these ureters is elongated, tortuous, and dilated. Endoscopically, the ureteral orifices are lateral, golf hole in appearance, and frequently associated with diverticulum. The distal ureter is characterized by asymmetric ectasia and more often involved than the proximal ureter. Secondary obstruction may occur from kinking and folding of the redundant ureter. Primary obstruction has been reported at the ureterovesical junction in a select group.[45] Histologically, there is an increase in fibrous tissue at the expense of normally developed ureteric muscle. Children with prune belly syndrome and vesicoureteral reflux have been reported to have an increased ratio of collagen to smooth muscle fibers in the muscularis.[46] This may help explain the poor dynamic characteristics of the ureter, resulting in ineffective peristalsis and urinary stagnation.[45] Degeneration of nonmyelinated Schwann fibers and a decreased number of nerve plexus may also contribute to decreased ureteral peristalsis.[47] Ureteric abnormalities tend to predominate in the distal portion of the ureter, an important concept to consider during operative intervention.

Nonrefluxing, Nonobstructed Megaureter

The nonrefluxing, nonobstructed megaureter is most often encountered in the neonate with the antenatal diagnosis of hydronephrosis. While the etiology remains in question, fetal renal physiology may play a role. Rapid changes in renal vascular resistance, glomerular filtration rate (GFR), and urinary concentration result in a four- to sixfold increase in urine production prior to birth. This increase in urine output may surpass the dynamic ability of the ureter to transmit the increased volume to the bladder, resulting in transient ureteral dilatation.

McLellan et al. report resolution of the nonrefluxing megaureter in the majority of children, with the time to resolution based on the initial grade of hydronephrosis. In children with grades 1–3, the hydronephrosis resolved at a median age of 13, 24, and 35 months, respectively, and in children with grades 4 and 5, it resolved at a median age of 48 months.[48]

Refluxing, Obstructed Megaureter

The refluxing, obstructed megaureter occurs due to ectopic insertion of the ureteral orifice in the region of the bladder neck. During bladder filling, the bladder neck is closed, acting as a distal obstruction. With voiding, the bladder neck opens and allows for reflux. A cyclic voiding cystourethrogram may be required for diagnosis in suspected cases.

DIAGNOSIS

The routine use of fetal sonography has dramatically increased the diagnosis of the megaureter. Brown et al. delineated the impact fetal sonography has had on identification of the megaureter.[49] Prior to fetal sonography, megaureter was diagnosed after the development of symptoms such as urinary tract infection, hematuria, and pain.[3] In the presonography era, clinically significant megaureters accounted for 8% of children found to have hydroureteronephrosis (ureteropelvic junction obstruction was noted in 22%, posterior urethral valves in 19%, and ectopic ureterocele in 14%).[49] With current routine use of fetal sonography, the incidence of the megaureter occurs in 23% of asymptomatic neonates and is only surpassed by hydronephrosis, which is seen in 41%.[49] This increased incidence can only be explained by more routine use and improved quality of fetal sonography. Even in the era of fetal sonography, Anderson and associates found that 17% of their patients with a primary megaureter presented with a history of pain, of which 10% had acute onset of severe pain.[50]

The percentage of children with asymptomatic megaureter who will eventually develop symptoms is unknown. Chertin et al. found on long-term follow-up that 31% of children diagnosed with a megaureter went on to surgical correction. Side and gender were not predictive, but grade of hydronephrosis (Society for Fetal Urology [SFU] grades 3 and 4), ureteral diameter of >1.33 cm, and renal function of <30% were all significant predictors of operative intervention.[51] Shukla and associates reported similar findings, with resolution of the megaureter in the majority of their patients and the rare incidence of problems occurring after 14 years of age.[52] Arena et al. found a similar rate of resolution and need for surgical intervention, noting that neonatally diagnosed megaureters typically improve within 3.6 years.[20]

EVALUATION

Ultrasonography

Ultrasonography plays a key role in the assessment of megaureter and is the primary imaging modality in the assessment of antenatal hydronephrosis and the initial imaging study obtained for symptomatic genitourinary abnormalities. Ultrasound can provide information regarding the size, shape, tortuosity, and bulbar appearance of the ureter, and also degree of dilatation of the renal pelvis and renal calyces. The course of the ureter can be traced from the renal pelvis to its distal insertion. Careful pelvic sonography can further detail the course of the distal ureter. The ureter may enter an obstructed ureterocele or end in an ectopic location within the bladder neck or posterior urethra. An obstructed distal segment may be recognized when a peristaltic wave of urine abruptly stops a few centimeters from the bladder and rebounds into the dilated proximal ureter (Figure 39.5). The echogenicity of the kidney is a helpful

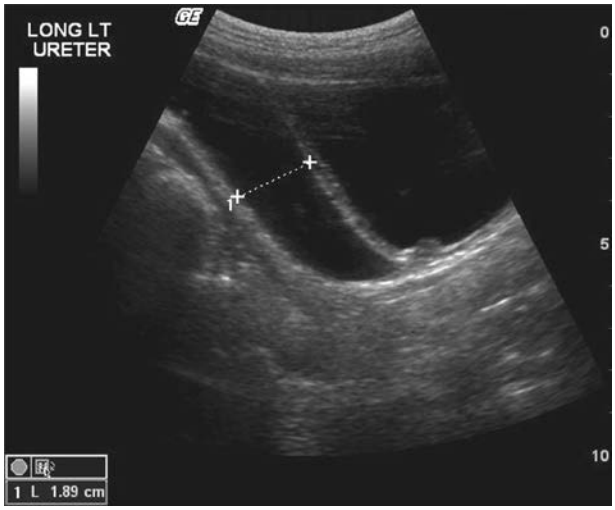

FIGURE 39.5 Sonographic appearance of the distal megaureter with a diminutive terminal segment.

parameter used to distinguish between an obstructive and unobstructive process, with increased echogenicity supporting obstruction.[53] A renal resistance index of >0.70 has been shown to correlate with obstruction. However, the utility of the resistance index in the pediatric population may be limited due to the lack of normalized standards for age.[54,55] Sonography, however, provides us with anatomic findings but lacks the ability to quantify a dynamic process, and the true significance of any abnormal megaureter must be determined by a functional imaging study.

Voiding Cystourethrography

Voiding cystourethrography is essential to rule out vesicoureteral reflux. A conventional fluoroscopic cystogram is preferred over a nuclear cystogram in that assessing the anatomic appearance of the bladder, bladder neck, urethra, and ureters is necessary for precise diagnosis and treatment. The cyclic voiding cystourethrogram is beneficial when an ectopic, sphincteric ureter is suspected. In this scenario, the ureter can be obstructed when the bladder is at rest and reflux only during the voiding phase. Blickman and Lebowitz characterize the obstructed, refluxing megaureter to have a markedly enlarged proximal ureter with a normal-appearing ureterovesical segment.[56]

Excretory Urography

Excretory urography and tomography are waning as diagnostic modalities in the evaluation of pediatric uropathy. Stool, bowel gas, and maturational immaturity of the neonatal kidney limit their utility. In addition, the degree of hydronephrosis noted does not equate to severity of obstruction. Rarely, when anatomic definition is required, excretory urography may play a role.[57]

Renography

Diuretic renal scintigraphy provides the greatest quantitative information of functional and dynamic data. The degree of obstruction can be determined by evaluating multiple parameters, including renal uptake, excretion, time to peak activity, and $T_{1/2}$ following lasix washout. Two of the more common radiotracers used to evaluate obstruction are TC-99m diethylenetriaminepentaacetic acid (DTPA) and TC-99m mercaptoacetyltriglycine (MAG3).[58,59] DTPA is a glomerular agent and provides limited information during the first month of life because of a low neonatal GFR. MAG3 is extracted by the kidney and dependent on effective renal plasma flow, not GFR. This results in less background artifact. These factors make MAG3 a more attractive agent during the neonatal period.[58]

Multiple variables affect data acquisition and interpretation. For that reason, renal scintigraphy must be performed in a standardized fashion using a protocol that optimizes the hydrational state, administration of diuretic, and acquisition of time–activity curves.[60] It is important to have a separate activity curve generated for the kidney and the ureter when assessing for an obstructive pattern. Isolating simply over the kidney can produce deceiving results, showing an acceptable washout of the radiotracer from the kidney without assessing washout from an obstructed ureter (Figure 39.6). Obtaining time–activity curves over the ureter will help confirm distal ureteral obstruction. The timing of diuretic administration can play a role in assessing $T_{1/2}$, with benefits attributed to administration at a standard time either before or after radiopharmaceutical administration.[61] Regardless of the protocol used, it is most important that consistent standards are maintained in order to compare successive studies in the same individual.

Magnetic Resonance Urography

Magnetic resonance urography (MRU) can be very helpful in the evaluation of the megaureter without the use of radiation (see Video 39.1). MRU with gadolinium has less nephrotoxic effects than contrast agents used for intravenous urography and conventional computed tomography (CT) imaging. With improved technology and the advent of open MRI scanners eliminating the need for anesthesia, this imaging modality may become the anatomic study of choice, particularly when renal compromise is present.[62–64,86]

Percutaneous Profusion Studies

Upper urinary tract urodynamic assessment can be helpful in difficult cases. The Whitaker test has traditionally been the procedure of choice.[66] However, the Whitaker test has limitations in the pediatric population. It is invasive and requires sedation for placement of a percutaneous renal catheter and bladder catheter. Whitaker described the test using a constant infusion of 10 cc per minute, with obstruction defined as an elevation in renal pressure greater than 22 cm H_2O over baseline.[66] The rate of infusion accommodated by the normal infant ureter is unknown. Infusing the renal pelvis at a rate of 10 cc/min may overcome the peristaltic flow potential of the normal infant or child's ureter, proving a false indicator for obstruction. A constant profusion of testing medium while recording the renal pelvic pressure may produce less artifact and be a more appropriate test.[67,68]

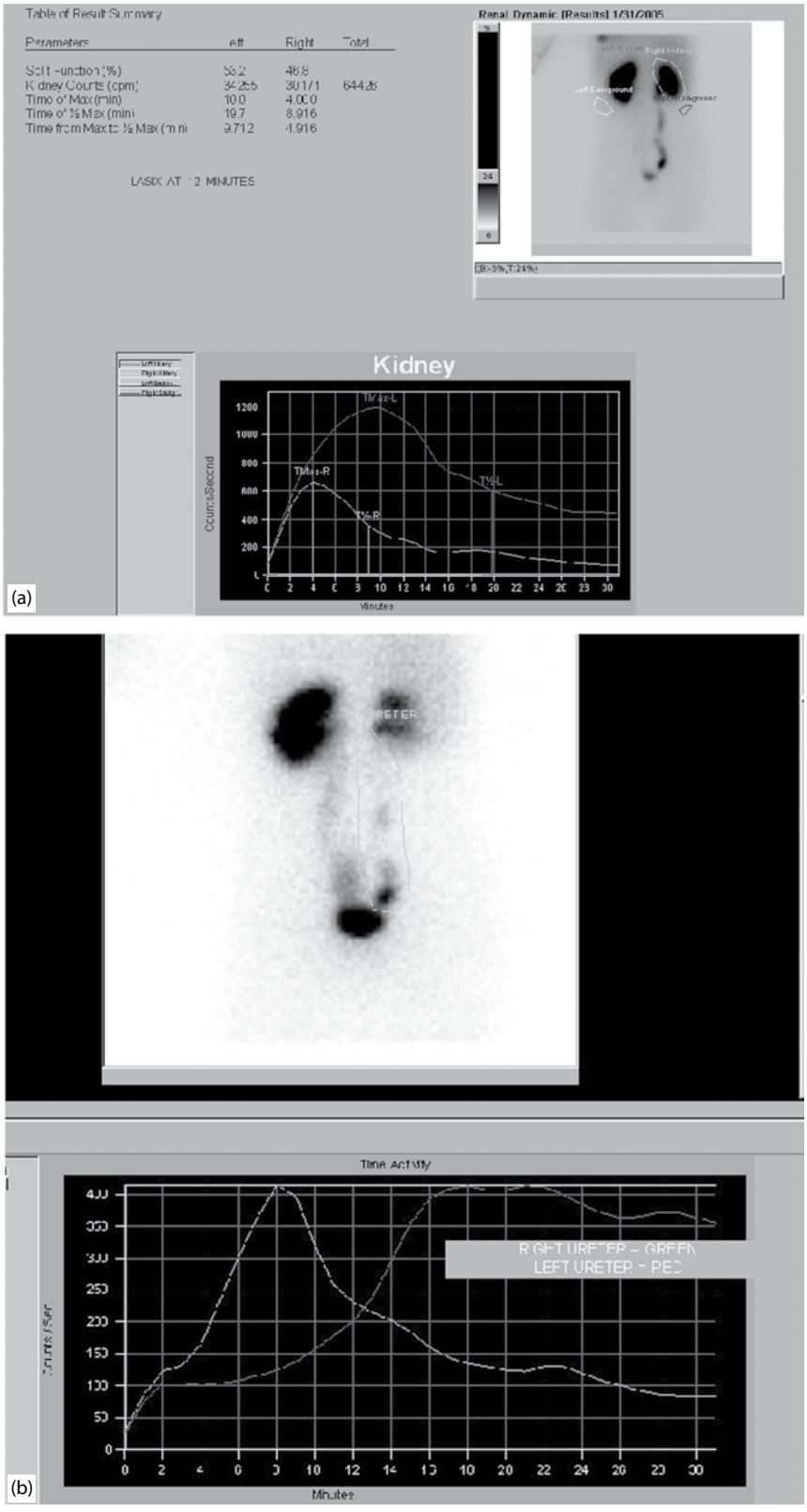

FIGURE 39.6 (a) MAG3 renal scan showing a composite pixel image and computer-generated kidney washout curve. There is relatively equal function with a delay in peak activity of the left system. The T½ washout of both kidneys is <20 minutes. (b) Right ureteral pixel image and curve indicating normal time–activity washout. The left ureteral time–activity curve shows an obstructive pattern with progressive accumulation and no washout.

Fung and associates explored ureteral opening pressure as a novel parameter for evaluating the obstructive nature of pediatric hydroureteronephrosis.[68] Renal pelvic pressure was assessed while simultaneously documenting the passage of contrast material from the distal ureter into the bladder. The infusion rate was individually calculated for each patient and maintained within a physiologically relevant range. A pressure increase of 14 cm H_20 within the renal pelvis was deemed consistent with distal ureteral obstruction. While this approach is invasive, it eliminates the problems of the infusion rate noted in the classic Whitaker study.[68]

DIFFERENTIAL TREATMENT

Therapeutic intervention of the megaureter is dependent on accurate classification. Secondary causes of a megaureter justify treatment of the primary problem, whether it is due to a neurogenic bladder, a posterior urethral membrane, ureterocele, diabetes insipidus, or a retroperitoneal process. Treatment of those problems are described elsewhere.

In general, a conservative approach can be taken in most cases of the megaureter.[18–20,51,52,69] There are no hard-core predictors for resolution. Improvement appears to be independent of gender, side, or bilaterality. A ureteral diameter greater than 1.33 cm and overall grade of hydroureteronephrosis (SFU grades 3 and 4) may be predictive of outcome.[51,70–72,93]

The role of antibiotic prophylaxis in megaureter is controversial.[72–74,93] Roth et al. reported a 4% risk of a urinary tract infection associated with an upper tract obstruction. This was not dependent on gender, level of obstruction, low grade, or circumcision status. The authors do not recommend the routing use of prophylaxis with nonrefluxing hydroureter with SFU grade 3–4 hydronephrosis.[75] Castagnetti and associates have explored the use of antibiotics and have identified children under the age of 6 months at the highest risk of developing symptomatic urinary tract infection, particularly if they undergo instrumentation.[73]

Refluxing Megaureter

Traditionally, grades 4/5 and 5/5 vesicoureteral reflux* have prompted operative intervention.[76] That approach may be appropriate for older children presenting with symptomatic urinary tract infections. However, there is growing evidence that operative intervention is not required in all neonates with refluxing megaureters, especially when identified during the workup of asymptomatic antenatal hydronephrosis. High-grade vesicoureteral reflux in neonates occurs more often in males than females, and improvement can occur during the first year of life.[76] There is little reason to proceed with early intervention, particularly when an infant has remained symptom-free on prophylactic medical management.

The association of megacystis–megaureter was first described by Williams in 1954[77] and is now well understood.[78] By definition, megacystis–megaureter is a large-capacity, thin-walled bladder with massive primary vesicoureteral reflux.[77,78] Megacystis–megaureter occurs in approximately 80% of boys diagnosed antenatally with bilateral reflux and found to have renal impairment.[79] The etiology of male predominance is unknown and does not appear to be due to bladder outlet obstruction. It is speculated that higher voiding pressure occurs in the male neonate. Children with megacystis–megaureter show progressive upper tract hydroureteronephrosis and bladder enlargement due to the recurrent cycling of urine into the upper tract during a detrusor contraction, followed by rapid refilling of the bladder upon relaxation of the detrusor after voiding. Over time, this cyclic event continually increases bladder volume and hydroureteronephrosis. In toilet-trained children, double voiding can temporize this process in children. Ten to fifteen minutes after the initial void, the child is encouraged to void again, allowing for an overall decrease in volume of retained urine. Positive effects of this technique occur first with stabilization of bladder volume, followed by reduction in bladder size and improvement of hydroureteronephrosis. Intermittent bladder catheterization can be an effective technique to eliminate residual urine in neonates and toddlers who are not toilet trained, allowing the child to reach an age where operative reconstruction would be beneficial. Ultimately, children with a megacystis–megaureter are best served by operative correction of the reflux.[78]

Nonrefluxing, Nonobstructed Megaureter

Approximately 6%–10% of neonates diagnosed with fetal sonography will have a nonrefluxing, nonobstructed megaureter.[80] A functional study is required to confirm adequate ureteral drainage. The initial medical management may be prophylactic antibiotics. Children with a nonrefluxing, nonobstructed megaureter maintain normal renal function, and the megaureter often reverts to normal.

Obstructed, Refluxing Megaureter

The obstructed, refluxing megaureter occurs due to a laterally positioned aperistaltic distal segment, or ectopic insertion of the ureter into the bladder neck or posterior urethra. While not emergent, operative correction of this entity is required in order to diminish the risk of upper urinary tract deterioration and to reduce the risk of urinary tract infections associated with obstruction.

Obstructed Megaureter

The indication for treatment of the obstructed megaureter prior to fetal sonography was relatively straightforward. Most children presented with a symptomatic urinary tract infection, abdominal pain, nausea, or vomiting and underwent repair.[3] Fetal sonography has identified a substantial number of neonates with an obstructed megaureter, many of whom will not have clinical symptoms. Current management of the obstructed megaureter is controversial.[17,81–84] Medical management, based on prophylactic antibiotics and watchful waiting, allows for potential spontaneous regression of the obstructed megaureter. Serial sonography will allow us to follow progression or resolution of hydronephrosis. Renal function must be objectively followed with renography in order to identify renal compromise.

* International study classification.

Repair of the infant megaureter is technically feasible but remains a challenge even in experienced hands. Secondary operative procedures have been reported as high as 10% when correcting an obstructed megaureter in an infant less than 8 months of age.[85] If possible, it is best to postpone repair of a megaureter until the child is older than 12 months of age, at which time technical hurdles are not as great.[86]

Occasionally, a neonate with an obstructed megaureter will present with severe renal compromise. In this situation, a distal cutaneous ureterostomy can provide temporary relief,[80] adequately draining the upper urinary tract and decreasing the risk of infection. The decompressed ureter may regain tone and a more normal caliber as the child grows and develops.[80]

OPERATIVE APPROACH

Temporary Diversion

A percutaneous nephrostomy is helpful when rapid drainage is required, and especially if the process involves both ureters with renal compromise. But small nephrostomy tubes are difficult to maintain longer than a few weeks. When prolonged drainage is required, a distal ureterostomy is appropriate. A pyelostomy can be undertaken, but it results in unnecessary proximal diversion when the pathology exists at the bladder level.

A cutaneous ureterostomy is practical for the severely obstructed neonatal megaureter. The procedure carries minimal morbidity, allows for rapid continuous decompression, and can often be performed in the outpatient setting. The ureter is approached through a 1.5–2 cm incision placed within an ipsilateral low inguinal skin crease. The muscles are separated and the space of Retzius entered. Identification of the ureter is facilitated when the bladder is partially full and usually easily visualized due to its size. Caution should be taken before opening the ureter because bowel can be mistaken for a distended ureter, particularly in the infant. When there is doubt, a 21-gauge needle should be used to aspirate the contents and confirm urine. If the ureter is not easily identified, the obliterated umbilical artery provides a suitable landmark for initiating the search. The ureter will often be found just beneath the transected obliterated umbilical artery. Once mobilized, a cutaneous loop ureterostomy provides adequate drainage. The ureter is secured to the anterior rectus fascia with a 4-0 or 5-0 absorbable suture and to the skin with the same. The size of the ureter prevents postoperative stenosis.

Definitive Reconstruction

The approach to the ureter for definitive urinary reconstruction can be either intravesical, extravesical, or combined. The dilated ureter is redundant and tortuous. Straightening and tapering the ureter without devascularization is required. The functional ability of the ureter to transmit urine into the bladder via peristalsis is inversely related to the size of the megaureter. In order to form an antirefluxing submucosal tunnel, the ureter is tapered to achieve a ureteral diameter that will allow for a 4–5:1 ratio of submucosal tunnel length to ureteral diameter. Enough ureter is mobilized in order to taper the intravesical ureter and a short portion of extravesical ureter. There should be a gradual transition from the tapered to dilated ureter to prevent a sharp gradient, which can act as a pseudo-obstruction. Multiple tailoring techniques exist for ureteral tapering and include ureteral imbrication and formal ureteral excision.[87–90,111]

The techniques described below are based on an open approach. However, the utility of minimally invasive alternatives, such as laparoscopic and robotically assisted procedures, has shown great promise and is gaining in popularity.[91–100] In addition, endoscopic procedures have been tried for primary obstructive megaureters utilizing high-pressure balloon dilatation of the distal ureteral or endoureterotomy, followed by several weeks (most commonly 8 weeks) of ureteral intubation with a ureteral stent.[129] Short-term success with improvement in hydroureteronephrosis and obstruction has been reported in 56%–100%, while postoperative vesicoureteral reflux has not been reported to be significant.[101–108] Longer follow-up will be required in order to determine long-term outcomes.

Imbrication

Ureteral imbrication is appropriate for marginally dilated ureters. Two common imbricating techniques include the Starr and Kalicinski plications.[87,88] In the Starr plication, a Lembert technique with a 6-0 absorbable suture is used to "fold in" the redundant ureter over a 10 or 12 Fr catheter[87] (Figure 39.7). Kalicinski established a plication technique that excludes the redundant ureter from the urinary system (Figure 39.8).[71,88] A 10 or 12 Fr catheter is used for a template, and an avascular segment of excess ureter is isolated. A running 5-0 or 6-0 absorbable suture follows the course of the ureter, separating it from the redundant segment. The redundant segment is then folded over the ureter and secured with a second absorbable suture layer (Figure 39.9). Regardless of the imbrication technique, the plicated ureter is brought into the bladder and the anastomosis with a submucosal tunnel is created in either a cross-trigonal or a Politano–Leadbetter fashion.

Ureteral stents may be placed for 3–7 days but are often unnecessary. The advantage of ureteral plication relates to preservation of the blood supply, a decreased incidence of devascularization, minimal risk of urinary leak, and infrequent obstruction. When massive ureteral dilatation is present, imbrication will add unwanted bulk, making the ureter difficult to reimplant, particularly if a bilateral procedure is performed. A variation to these two primary techniques has been reported to reduce the ureteral caliber while preserving the ureteral blood supply, and eliminating the problem of bulk.[109]

Excisional Tapering

Formal excisional tapering of the ureter is required for extremely bulky ureters or a bilateral process. Hendren pioneered ureteral remodeling, and the technique has stood the test of time.[89] The ureter is loosely tapered over a 10 or 12 Fr catheter, depending on the child's age and size. Straight Allis clamps are placed longitudinally along the ureter in a region of least vascularity. Angled Allis

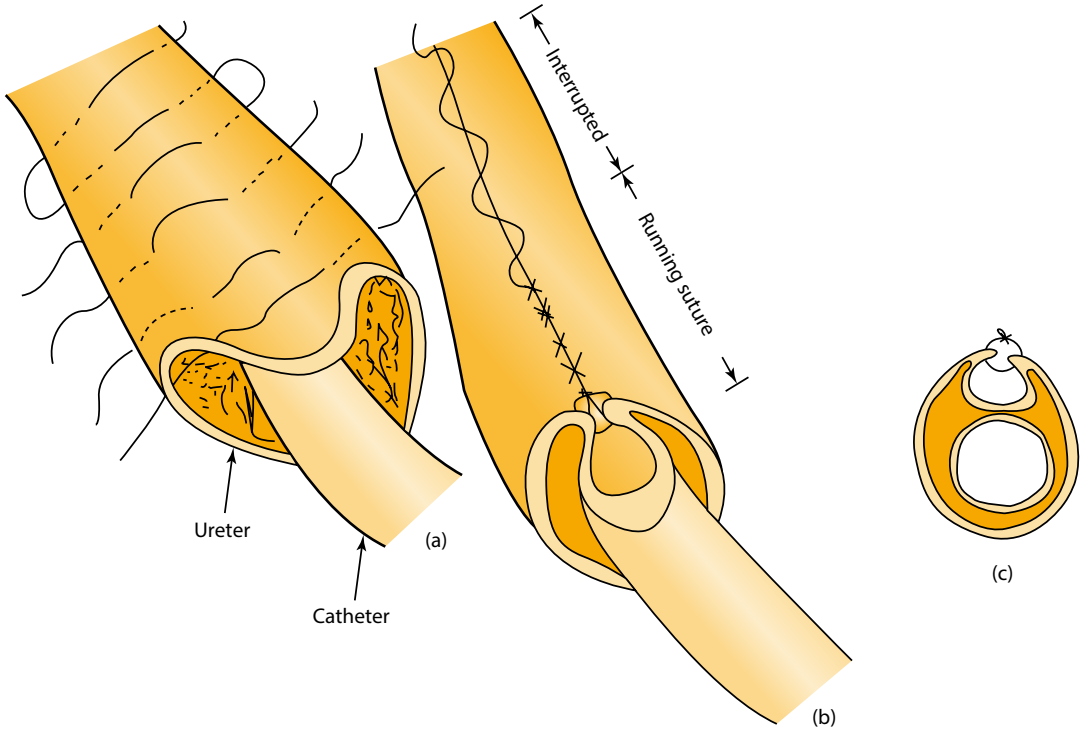

FIGURE 39.7 Starr technique of ureteral imbrication. (a) The ureter is folded inward over a 10 or 12 Fr catheter as a guide. (b) The distal portion is secured with interrupted sutures to allow for transection without compromising the running suture line. (c) Cross section of (b).

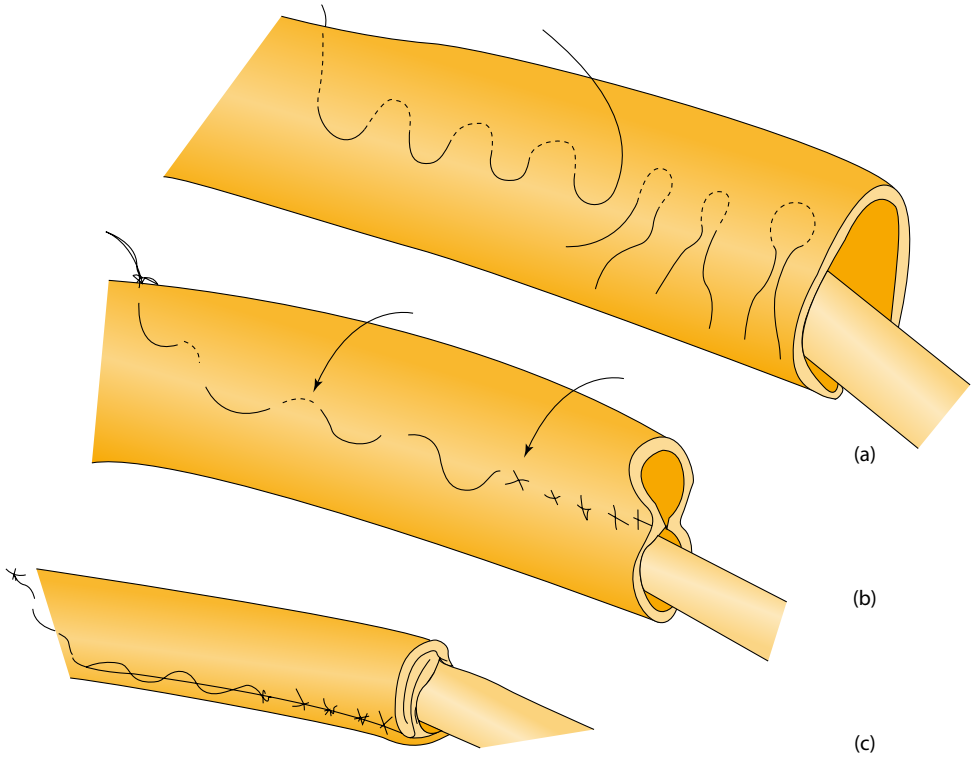

FIGURE 39.8 Kalicinski technique of ureteral imbrication. (a) The excess segment of ureter is excluded from the flow of urine. (b) It is then folded over the ureter using a 10 or 12 Fr catheter as a guide. (c) The distal portion is secured with interrupted sutures to allow for transection.

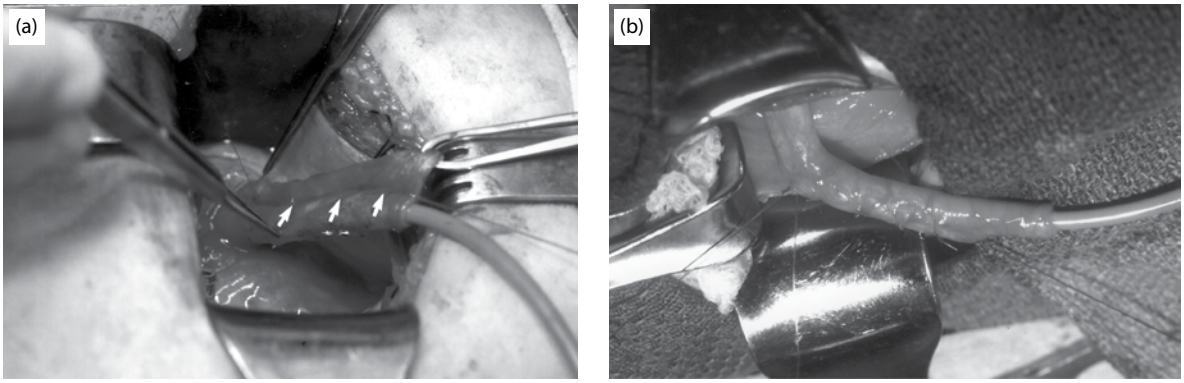

FIGURE 39.9 (a) Kalicinski plication technique isolating the redundant ureter from the distal flow of urine (arrows). (b) The excluded segment has been folded and secured to the distal ureter. (Adapted from Joseph DB, Ureterovesical junction anomalies—megaureters. In. Gearhart JP, Rink RC, Mouriquand PDE eds., *Pediatric Urology*, WB Saunders: Philadelphia, 2000, p. 355.)

clamps are then placed over the ureter securing the internal 10–12 Fr catheter (Figure 39.10). Care is used to prevent the temptation of excluding too much redundant ureter, which results in excessive tapering around the catheter. The ureter is closed in two layers. First, a running, locking 5-0 or 6-0 absorbable suture directly opposes the mucosa and the muscularis of the ureter. The locking technique limits ureteral reefing and decreases extravasation. A second running adventitial layer of absorbable suture decreases leaking. Both running layers stop a few centimeters from the distal end of the ureter. The very distal portion of the ureter is closed in two layers with interrupted sutures. This allows for excision of the distal ureter if required without interruption of the running suture line. A ureteral stent can be placed to decrease urinary extravasation. Stenting also provides a scaffold for the ureter to conform to during the postoperative period, helping to prevent kinking and bypassing the tapered region, which initially may act as an obstruction due to postoperative edema. The ureter may be stented 7–14 days. The necessity for periureteral drainage in the form of a Penrose drain or a Jackson–Pratt drain is variable, dependent on the technique used for ureteral tailoring and the presence of a ureteral stent. Periureteral drainage may be helpful when a ureteral stent has not been placed and a substantial portion of tapered distal ureter remains extravesical.

In most situations, only the portion of the distal ureter that is going to be placed within the bladder and 1 or 2 cm beyond needs to be tapered. There should be a gentle transition from the ureteral hiatus at the bladder to the nontapered ureter. Proximal ureteral tapering is rarely required and is limited to children with persisting proximal hydroureteronephrosis, with an obstructed pattern in the face of a patent distal ureter.[90]

In complex reconstructive cases, consideration should be given to a transureteroureterostomy and a unilateral tapered reimplant, particularly when there is a small bladder.

POSTOPERATIVE MANAGEMENT

Removal of the ureteral stent is dependent on the procedure performed. The stent can be removed 3–7 days after imbrication, and 7–14 days following an excisional repair. Some use a JJ ureteral stent, but this requires a second anesthetic for removal, usually around 4–6 weeks after surgery. Ureterograms at the time of stent removal are not necessarily beneficial. Postoperative edema can limit drainage, giving

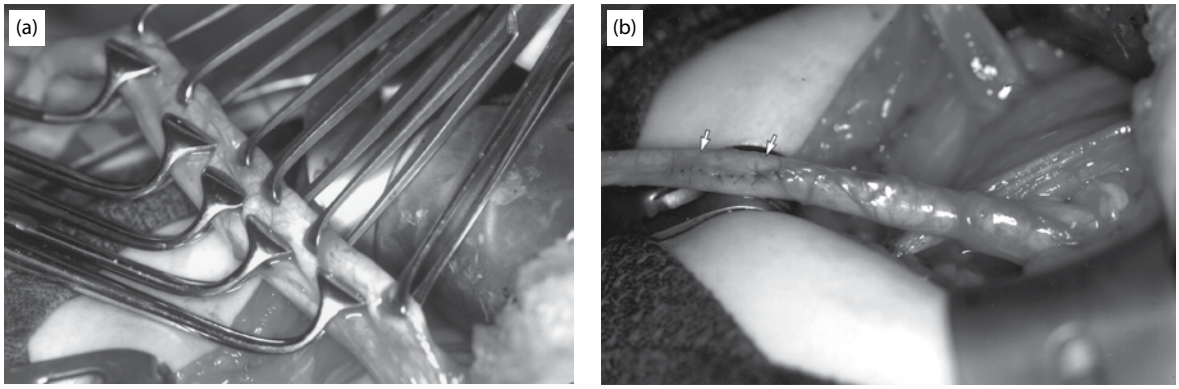

FIGURE 39.10 (a) Angled Hendren clamps placed loosely over a 10 or 12 Fr catheter securing the retained portion of the distal ureter. Straight Allis clamps isolate the segment to be excised. (b) A two-layer technique is used to close the ureter, interrupting the distal-most portion and allowing for excision as needed. The arrow indicates the interrupted portion. (Adapted from Joseph DB, Ureterovesical junction anomalies—megaureters. In. Gearhart JP, Rink RC, Mouriquand PDE eds., *Pediatric Urology*, WB Saunders: Philadelphia, 2000, p. 356.)

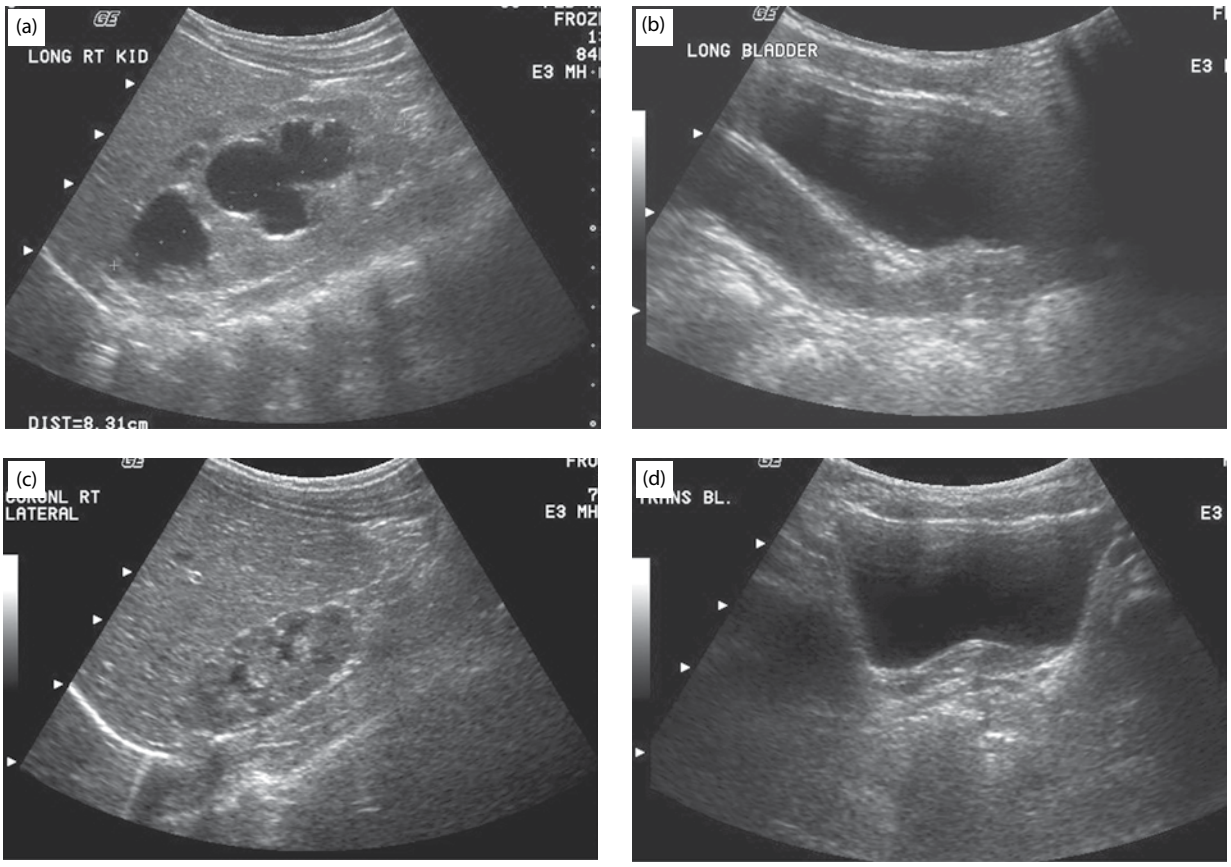

FIGURE 39.11 6 weeks following repair of a right refluxing megaureter revealing (a) right hydronephrosis and (b) right hydroureter. Ultrasound sound at 3 months postop shows resolution of right hydronephrosis (c) and megaureter (d).

the appearance of a high-grade obstruction when, in fact, removal of the stent is all that is required. Administration of a broad-spectrum antibiotic prior to removing a stent decreases the possibility of urosepsis even when the child has been maintained on prophylactic antibiotics.

Postoperative ureteral edema can persist for 6 weeks. Imaging studies, either sonography or renal scintigraphy, should be avoided during that time. The initial images on sonography may show increased hydronephrosis and proximal hydroureter when compared with preoperative sonographic imaging, particularly when repairing a refluxing megaureter (Figure 39.11). This is due to the compliant proximal ureter and relative resistance of flow through the tapered segment. It is important to review the ureteral size on the preoperative cystogram to help determine the significance of postoperative sonographic dilatation. Renal scintigraphy should be used to assess for postoperative obstruction in troublesome cases.

A postoperative voiding cystourethrogram at 6 months is performed to confirm the absence of vesicoureteral reflux. Prophylactic antibiotics can be discontinued with resolution of the reflux.

COMPLICATIONS

Successful operative outcomes of megaureter reconstruction have been reported to be 93%–95% for imbrication[85,88,110–114] and 74%–90% for excisional tapering.[85,110,112,115–118] Overall, the complication rate and morbidity are greater for a tapered procedure than for a nontapered ureteroneocystostomy. The two most common complications are obstruction and persisting reflux.

Postoperative complications are not simply due to technical error, inherent ureteral characteristics, and bladder dysfunction. A higher rate of postoperative vesicoureteral reflux may also be secondary to increased collagen deposition and altered smooth muscle.[33,41]

Postoperative edema can lead to obstruction requiring temporary percutaneous nephrostomy diversion. Physician patience is prudent to allow for the operative edema to subside, which might take 2–3 months. Persistent obstruction is likely due to ureteral ischemia and will ultimately require revision.

Persisting vesicoureteral reflux has been reported to occur in approximately 5% of tapered reimplants.[85,88,110–120] Transient mild reflux noted at 6 months can resolve spontaneously with time. Reflux persisting more than 3 years after surgery is unlikely to improve.[85] When significant and symptomatic, secondary corrective intervention is required; salvage endoscopic procedures using ureteral bulking agents have been successful.[121–123] When a reoperative procedure is performed, attention must be paid to preserving the ureteral blood supply and maximizing the ratio of the ureteral tunnel length to the diameter to at least 5:1. In situ ureteral tailoring

is an appealing alternative to a formal excisional repair. It achieves a gradual decrease in intraluminal diameter without compromising vascularity and avoids the difficult ureteral dissection. This should be considered in cases when the ureteral tunnel length had been maximized at the first encounter.[119]

Contralateral reflux may occur more often following repair of the refluxing megaureter than the obstructed megaureter. It has been suggested that the functional anatomy of the trigone is impaired in reflux but not obstruction.[124]

SUMMARY

The asymptomatic megaureter is commonly encountered due to the routine use of fetal sonography. The natural history of the megaureter supports observation and nonoperative management of most infants. When operative management is required, precise classification of the pathophysiology, along with intervention by a pediatric specialist, should result in a successful outcome.

MULTIMEDIA FILES AVAILABLE ONLINE (www.crcpress.com/cw/Docimo)

VIDEO 39.1 Megaureter MRU.

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CHAPTER 40

Ureteral Duplication Anomalies: Ectopic Ureters and Ureteroceles

Michael A. Keating

INTRODUCTION

Ureteral duplication is one of the most common anomalies affecting the genitourinary tract. A spectrum of involvement and clinical presentations exists, at times offering pediatric urologists with some of their more challenging diagnostic and therapeutic dilemmas. Common variations, including incomplete ureteral duplication and complete duplications with normally developed ureters and renal moieties, constitute the vast majority. As such, they represent no more than radiologic curiosities. Anomalies with clinical significance, including ectopic ureters and ureteroceles, are much less common. Historically, the majority of these probably remained clinically silent.[1,2] A smaller portion became evident as a consequence of hydronephrosis, vesicoureteral reflux (VUR), or incontinence, either in combination or alone. More recently, antenatal diagnosis has uncovered a large number of urologic anomalies, including different variants of ureteral duplications, that are asymptomatic. Antenatal detection enables the preservation of renal function and the avoidance of illness for some children. For others, perinatal identification creates controversy by introducing a large group of abnormalities that might have gone harmlessly undetected in the past.

Despite these decision-making dilemmas, it seems prudent to institute preemptive therapy for urinary tract anomalies that pose a risk to the affected child, until those characteristics that typify their spontaneous resolution or a lifetime free of urologic problems are better defined. Spontaneous resolution of most ectopic ureters and ureteroceles seems unlikely. As a consequence, pediatric urologic surgeons must remain familiar with the natural history of duplication anomalies, well versed in the evolving recommendations for their management, and familiar with the variety of surgical techniques available for their reconstruction. Ectopic ureters and ureteroceles represent distinct entities. However, they also appear to represent variations along the same general mechanisms in development. These result in differences in appearance but a number of common clinic features that, in some cases, offer similar paradigms in management.

EMBRYOLOGIC CONSIDERATIONS

Normal Development

A review of normal development provides the basis for understanding the pathophysiology of anomalies of the ureter and, in some cases, aids in their diagnosis and clinical management.

Ureteral development coincides with that of the kidney between the fourth and eighth weeks of gestation. The *ureteral bud (metanephric duct)* projects from the *Wolffian (mesonephric) duct* just proximal to its junction with the cloaca (Figure 40.1). As the ureteral bud elongates in a cephalad direction, it penetrates the adjacent metanephric tissue and divides into the calyces and collecting ducts. Proper fusion of the bud and the nephrogenic blastema is critical to tubular maturation within the renal anlage and ultimate function of the kidney. Mesenchymal–epithelial interactions, perhaps under the influence of local paracrine factors acting via receptors on the ducts, help pattern normal formation.[3]

The segment of the Wolffian duct between the cloaca and the takeoff of the ureteral bud (the future ureteral orifice) is called the *common excretory duct*. The migration of tissue that occurs during the excretory duct's replacement or incorporation into the urogenital sinus helps to explain the variable relationships that sometimes occur between the ureters and the trigone of the bladder, and genital ducts. Conceptually, these events represent some of the most difficult to understand in urinary tract embryology.

In the classic description, as the common excretory duct is absorbed into the bladder, the ureteral orifice migrates in a cranial and lateral direction. While this occurs, the excretory duct migrates to the midline and fuses with its contralateral partner to form the primitive trigone. This would explain a presumed mesodermal origin of the trigone and, depending on its relationship with the mesonephric and ureteral buds, ureteral location. However, recent studies have suggested that the trigone may instead be endodermal in origin.[4,5] Regression of the common excretory duct occurs through apoptosis. Formation of the trigone then occurs as the excretory duct is replaced by endoderm, with expansion of trigone dictating ureteral bud location.

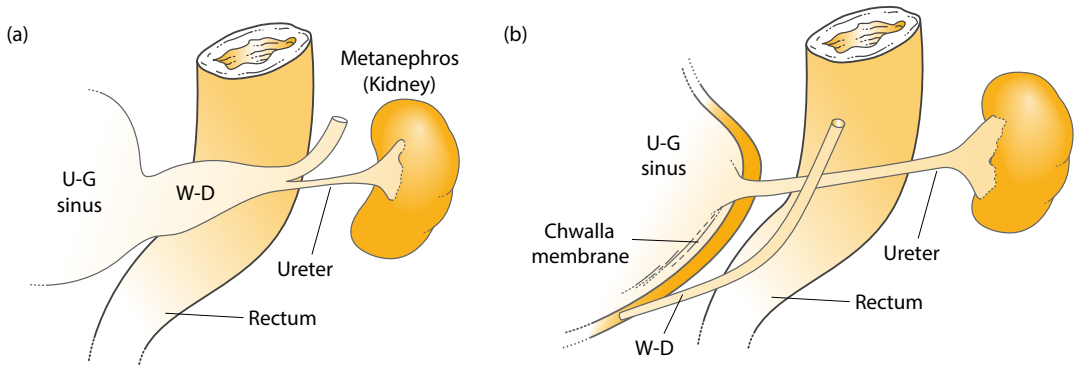


FIGURE 40.1 (a and b) Relationships of ureteral bud, Wolffian (mesonephric) duct (W-D), and urogential sinus (U-G). The segment of the Wolffian duct between the urogenital sinus and ureteral bud represents the common excretory duct.

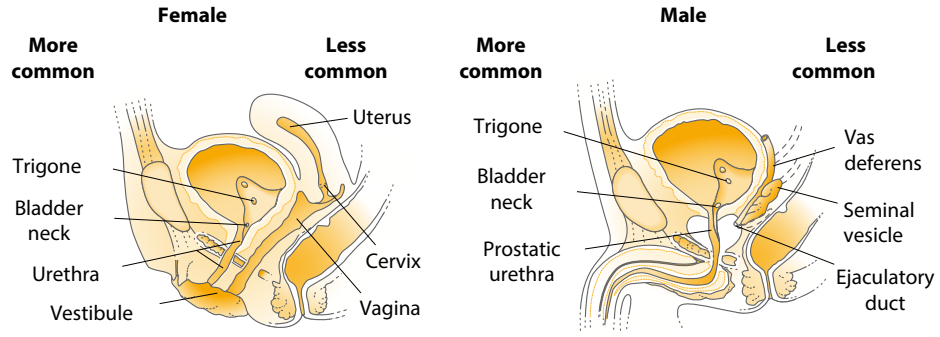


FIGURE 40.2 Anatomic locations of ectopic ureters.

Regardless of the mechanism, the orifice of the Wolffian (mesonephric) duct ends in a caudal and medial position at the utricle. The Wolffian duct ultimately differentiates into the prostate, seminal vesicles, vas deferens, and epididymis in males. In females, the Wolffian ducts guide the Mullerian ducts into position in the midline, where the latter fuse to form the uterus, proximal vagina, and fallopian tubes. After their involution, Wolffian remnants persist in as many as 25% of women as Gartner's duct lying along the anterolateral vaginal wall and uterus, and the epoophoron and oophoron within the broad ligament supporting the fallopian tubes.

Explanations for the variety of anomalies that affect the ureter have their basis in this developmental progression, although the causes of the initial insults remain unclear.[6] An alteration in complex temporal–spatial timing seems indisputable.

Abnormal Development

Lateral ectopia occurs when the ureteral bud originates from a more caudal position than usual on the mesonephric duct, for reasons that remain to be defined. As a result, the ureteral orifice has more time to be absorbed within the bladder and to begin its cranial and lateral migration. As the degree of laterality becomes more exaggerated, the length of the submucosal ureter is progressively shortened. In addition, because the common excretory duct is shortened by the premature takeoff of the ureteral bud, its mesenchymal contribution to the trigone is blunted. This results in muscular deficiency of the trigonal–ureteral complex. Primary reflux becomes a common consequence of lateral ectopia and is thoroughly discussed elsewhere (see Chapter X on vesicoureteral reflux).

Caudal ectopia of the ureter results from an abnormally high takeoff of the ureteral bud. This allows less time for the orifice to be absorbed into the bladder. Now more closely positioned to ductal tissue typically destined to become Wolffian, the ureter arrives in a medial trigonal or urethral position or is extravesically positioned along the path of Wolffian structures or remnants. The location of Wolffian remnants helps explain an important difference in presentation of ectopic ureters between males and females (Figure 40.2). *Ectopic ureters in males are connected to structures that continue to drain into the bladder proximal to the urinary sphincter.* Urinary control should be normal. In contrast, ectopic ureters in females potentially vent into remnants adjacent to the fallopian tube (epoophoron), body of the uterus (paroophoron), and vagina (Gartner's duct), where they presumably rupture or are absorbed. Since the urinary sphincter is bypassed, incontinence results.

Ureteral duplications occur when a single ureteral bud branches prematurely during its ascent or when two distinct ureteral buds arise from the Wolffian (mesonephric) duct (Figure 40.3). The clinical significance of these anomalies depends on the location of the buds and their interplay with the developing kidney.

An incomplete ureteral duplication results if a single ureteral bud branches after its takeoff from the

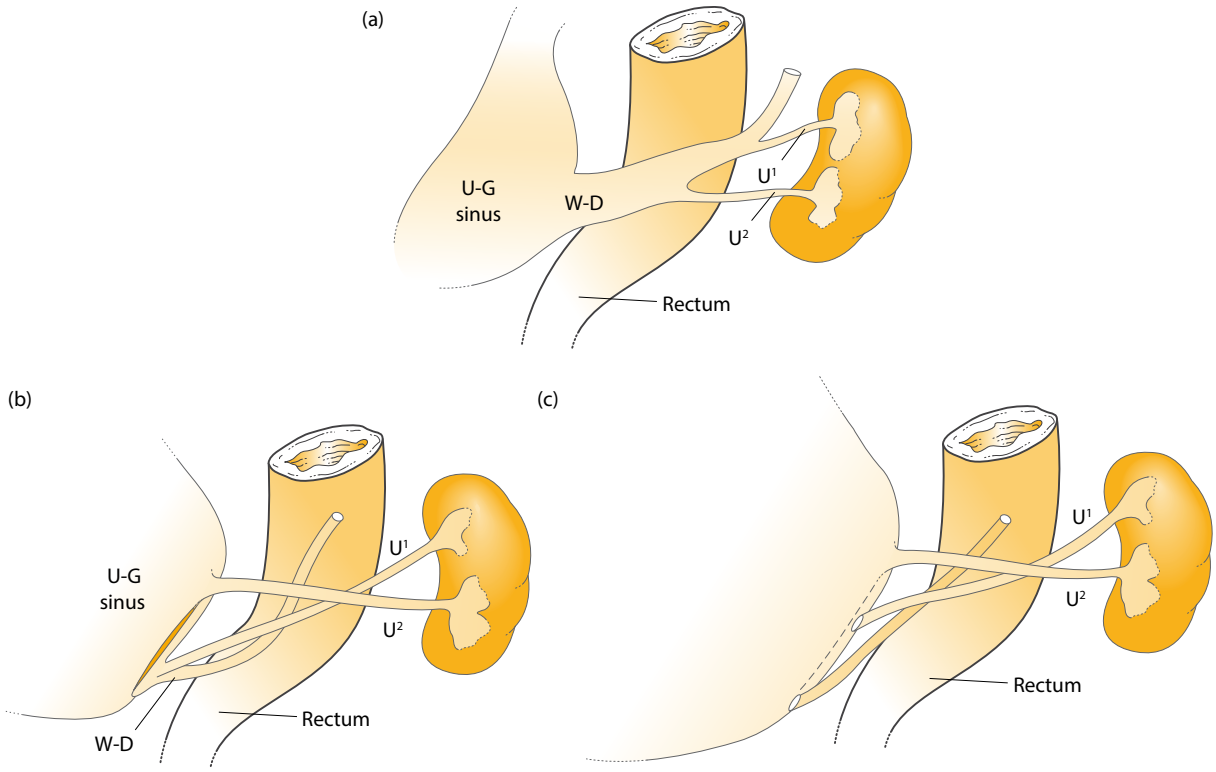


FIGURE 40.3 Complete ureteral duplication. *Caudal ectopia* (U^1) results from an abnormally high takeoff of the ureteral bud, which remains positioned near Wolffian duct tissue. *Lateral ectopia* (U^2) results from a more caudal position, allowing more time for intravesical migration.

mesonephric duct. The configurations that can occur range from anomalies as mild as a bifid renal pelvis (late branching) to nearly complete duplications having a common intravesical stem (early branching). The location of the ureteral orifice with incomplete duplications depends on the takeoff of the ureteral bud in the sequence cited above. Bifurcation can occur at any level from the bladder to the renal pelvis but can begin in the lower third of the ureter.[7] Most buds are normally positioned along the mesonephric duct, and as a consequence, incomplete duplications are usually radiologic curiosities having little clinical significance.

Complete ureteral duplication occurs when two ureteral buds project from the mesonephric duct, each having a separate interaction with the metanephric blastema. During their early takeoff, the buds interact with the primordial kidney in logical fashion. The most superior or cephalad bud induces the upper portion of the blastema (upper pole), while the lower bud joins the lower-pole moiety. However, *the ultimate positions of the ureteral orifices are governed by the same enigmatic rules of tissue migration and incorporation into the bladder described for singlets* above.

When both buds are close together and project from an acceptable position along the mesonephric duct, both ureters will have normally positioned orifices. When the buds are more widely separated, one or both will be ectopic. *If the superior or upper-pole bud projects from an abnormally high position along the mesonephric duct, caudal ectopia is the outcome. If the bud to the lower pole originates from a more caudal position along the duct, lateral ectopia results*. To achieve their ultimate positions, the ureters and their orifices complete a 180° clockwise rotation along their longitudinal axes. These relationships, defined by the *Weigert–Meyer law*, are unusually consistent.[8,9] Exceptions have been described but are rare.[10,11]

The molecular and hormonal basis of the epithelial–mesenchymal interplay of the ureteral bud and developing renal blastema are discussed elsewhere (see Chapter X on embryology). A polygenic mode of inheritance is suggested for ureteral abnormalities. Similarities in renal development to the relationships defined by Mackie and Stephens (below) have been correlated with these more complex studies.

Ureteroceles

Several theories have been proposed for the development of ureteroceles, although their etiology remains unclear. Some of the more popular theories are

1. *Persistence of Chwalle's membrane*, which is a two-layered membrane that transiently separates the caudal end of the Wolffian duct from the urogenital sinus (37 days gestation),[12] is possible. Incomplete dissolution of the membrane could account for the cystic dilatation of the terminal ureter and stenosis of the orifice found with ureteroceles. A delay in the apoptosis felt to occur between the ureteral bud and developing trigone may be implicated.[5]
2. *Abnormal muscular development* of the terminal ureter has been implicated by a number of studies.[13]

Ballooning of the distal ureter could be explained by a deficiency or an absence of its muscular investing layers, a finding shown in more than 90% of specimens in one study.[14] By comparison, the distal segments of ectopic ureters consistently have better developed musculature than ureteroceles.[15] The ureterocele itself is covered with vesical mucosa, whereas its internal lining is made up of ureteral mucosa. Varying degrees of attenuated smooth muscle and connective tissue are sandwiched between. *An element of meatal or perisphincteric obstruction*[16] *may contribute to the dilatation*. However, some ureteroceles present without a functioning kidney, suggesting to some clinicians that urinary output is an unnecessary impetus to distal ureteral ectasia.[17] It is also plausible that the kidneys associated with these so-called "blind ureteroceles" produce urine during an early critical stage in development but subsequently involute.[18]

3. *Abnormal widening of the mesonephric duct* may occur in the segment between its insertion at the urogenital sinus and the ureteral bud. This area normally dilates in concert with an undefined stimulus for vesical and urethral expansion. Ureteral migration is presumably completed before this expansion occurs. *Proximal extension of the widening process into the distal ureter* could result in ureterocele development.[6] This explanation seems plausible for intravesical ureteroceles, the ureter and orifice of which have migrated appropriately. *Late incorporation of the ureteral bud from an abnormally proximal position* within this dilated segment is another possibility. This explanation is more compatible with extravesical ureteroceles accompanied by ectopic orifices. Notably, ectopic ureters associated with even more proximal buds that insert into Wolffian remnants are rarely ectatic at their distal ends. They are presumably unaffected by the stimulus that alters the urogenital sinus.[13]
4. *Defective ureteral maturation* affecting the detachment of the ureteral bud from the mesonephric duct as it moves into the bladder has been suggested in mouse models.[5] As discussed below, the concept of abnormal bud position may also account for the renal dysplasia that accompanies many extravesical ureteroceles.

URETERAL–RENAL INTERACTIONS

The ultimate maturation of the renal blastema is dictated by its interaction with the ureteral bud. When this interplay is experimentally altered, the transformation expected of blastema to normal nephron does not occur.[19,20] Mackie and Stephens[21] proposed the midregion of the elongate metanephric blastema as being most conducive to becoming normal renal parenchyma. *Ureteral buds that originate from abnormally cephalic or caudal positions along the Wolffian duct are destined to induce polar blastema, which results in cystic dysplasia* (Figure 40.4). This theory offers a ready explanation for the dysplasia and scars found within kidneys with associated VUR where urinary tract infections (UTIs) have never occurred. It could also explain why ectopic ureters with urinary insertions

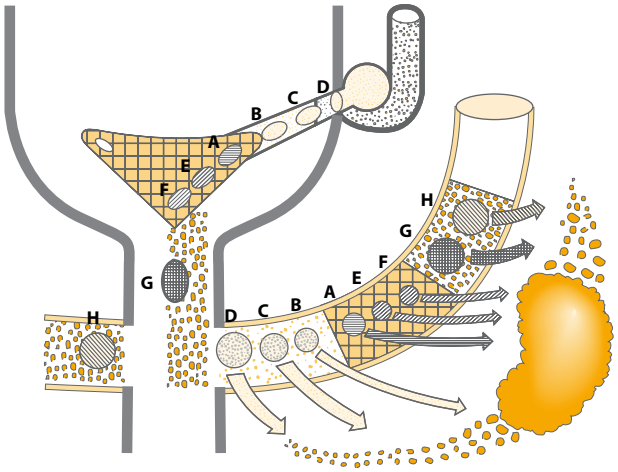


FIGURE 40.4 In theory, the position of the ureteral bud on the Wolffian (mesonephric) duct corresponds to the final position of the ureteral orifice and differentiation of the metanephric blastema. Lateral and caudal ectopia can both result in renal dysplasia.

(GU-ectopy) are more likely to be associated with functioning renal parenchyma than ectopic ureters having Wolffian or gynecologic (GYN-ectopy) insertions, where dysplasia is often present.[22] Ureteral bud takeoff could also explain the difference between the salvageable renal function usually seen with intravesical ureteroceles and the poor function that occurs with extravesical ureteroceles.

Clinical correlates offer only guarded support of this theory, despite its attractiveness. Most studies generally cite poor renal function in the presence of severe reflux or marked ureteral ectopia,[23] although the difference between GU- and GYN-ectopy has come into question.[24] In addition, antenatal detection has added some new twists. In one review of specimens from 50 consecutive patients undergoing partial nephrectomies, dysplasia was seen in 70% from ureteroceles and 30% from ectopic ureters.[25] Each had been diagnosed antenatally, yet none were felt to have histological changes that may have benefited from renal preservation surgery. In contrast, in a similar series of 40 consecutive antenatally diagnosed duplication anomalies, only 6 required heminephrectomy because of poor function, and none of these showed evidence of dyplasia.[26]

Most historical reports cite renal function with only 20%–30% of ureteroceles. This pales next to the yield of contemporary series, whose numbers are inflated by the addition of antenatally diagnosed anomalies and the sensitivity of better diagnostics. The clinical implications are obvious (see the "Recommendations for Management: Ectopic Ureters" section). Are these renal moieties previously destined to lose renal function as a consequence of progressive obstruction? Do they benefit from being surgically diverted or endoscopically decompressed? Or is renal parenchyma being preserved that has an intrinsic developmental insult? Nodular renal blastema has been reported in upper-pole nephrectomy specimens removed with ectopic ureteroceles.[27] Dysplasia is also a common finding.[28] The study by Arena et al.[29] failed to show any evidence of reversible histologic changes in partial nephrectomy

specimens of patients whose ureteroceles had been prenatally diagnosed. It is unclear as to whether this is cause for concern. To date, no chronic complications of retained renal segments have been reported (hypertension or tumor formation, for example).

NOMENCLATURE AND CLASSIFICATIONS

Ectopic Ureters

The term *ectopic ureter* refers to a ureter that has migrated with the Wolffian duct structures and is more caudally positioned than a normal ureter. With a duplex system, this is invariably the upper-pole ureter. By definition, such ureters drain beyond the bladder neck into the urethra, Wolffian, or Mullerian structures. The ureter to the lower pole of a duplication, which is sometimes laterally displaced and ectopic in the purest sense, is regarded as orthotopic. Single-system ureters, which are laterally misplaced and reflux as a consequence, are discussed elsewhere (see Chapter 42 on vesicoureteral reflux).

Ureteroceles

Historically, ureteroceles associated with single systems were regarded as *orthotopic* or *simple* and considered adult type, despite the fact that some such variants are clearly ectopic and occur in children (Figures 40.5 through 40.9). Ureteroceles subtending the upper-pole ureter of a duplex system have been described as *ectopic* and pediatric, although exceptions to both descriptions also commonly occur.[30] Gonzales[31] felt it simplest to describe the anomaly based on the location of its orifice. Other than their association *with a single or duplex*

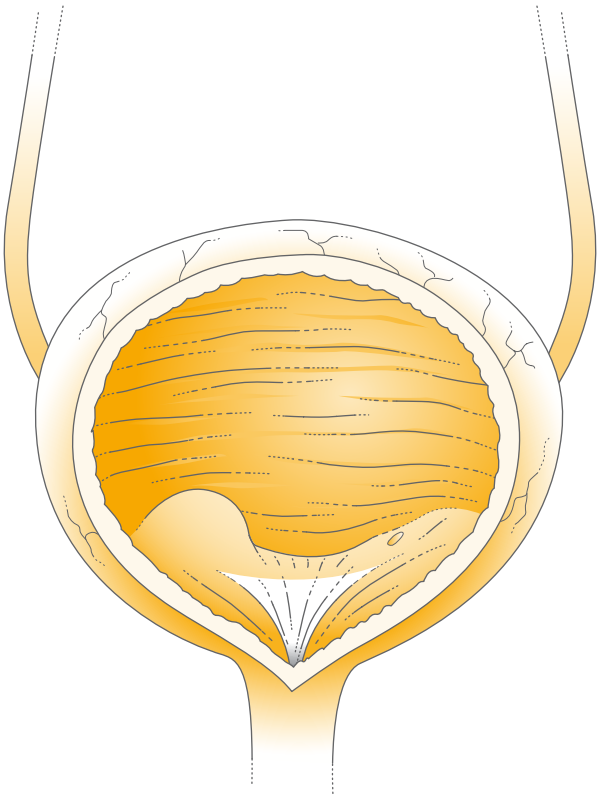


FIGURE 40.5 Intravesical ureterocele subtending a single ureter. This could also be classified as orthotopic or simple.

FIGURE 40.6 Excretory urogram showing bilateral single-system intravesical ureteroceles. Right is larger than left. Renal function is typically preserved.

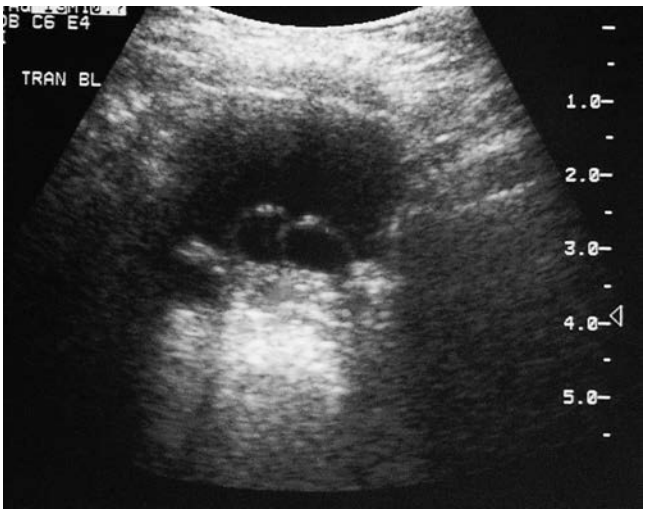


FIGURE 40.7 Ultrasonic appearance of similar patient with bilateral intravesical ureteroceles.

FIGURE 40.8 Intraoperative photograph of bilateral intravesical single-system ureteroceles.

system, two types of ureteroceles exist, *intravesical or extravesical*. This approach avoids the confusion associated with the terms *ectopic* and *orthotopic*. In addition, such nomenclature reflects the embryologic importance of the ureteral bud or orifice to renal development and distortion of the bladder neck. However, this form of categorization potentially mislabels ureteroceles with an intravesical orifice but an extension into the bladder neck or urethra. Anatomically, these too could be considered extravesical.

A variety of other classification schemes have been proposed for ureteroceles, although no system has been adopted universally. Stephens's[16] categorization can be used to provide additional information about the location

FIGURE 40.9 Large ureterocele extending toward the bladder neck (top). Catheter is in the lower-pole ureter, which is displaced and freely refluxes.

and configuration of the orifice of the ureterocele. These factors presumably account for the degree of distortion of the bladder neck and urethra, as well as the extensiveness of the renal dysplasia accompanying the anomaly (Table 40.1, Figures 40.10 and 40.11).

TABLE 40.1 Classification of duplex ureteroceles

Intravesical
Stenotic—40%: Involve a congenitally small ureteral orifice adding an element of obstruction for the upper pole.
Nonobstructed—5%: The ureteral orifice is large and balloons open without any ureteral obstruction.
Extravesical
Sphincteric—40%: The orifice opens outside the bladder and the ureterocele extends into the bladder neck and urethra. The orifice is normal or large and usually opens proximal to the external sphincter. In females, the meatus may open distal to the sphincter. At rest, the bladder neck and sphincter contract on the ureter and orifice, causing obstruction.
Sphincterostenotic—5%: Similar to sphincteric, although the ureteral orifice is stenotic.
Cecoureteroceles—5%: A large orifice opens in the bladder, but a blind pouch or cecum extends into the submucosa of the urethra. When the cecum distends with urine, urethral obstruction can result.
Blind ectopic—5%: Similar to sphincteric, with no ureteral orifice.

Source: Stephens FD. *Aust N Z J Surg* 1971;40:239.

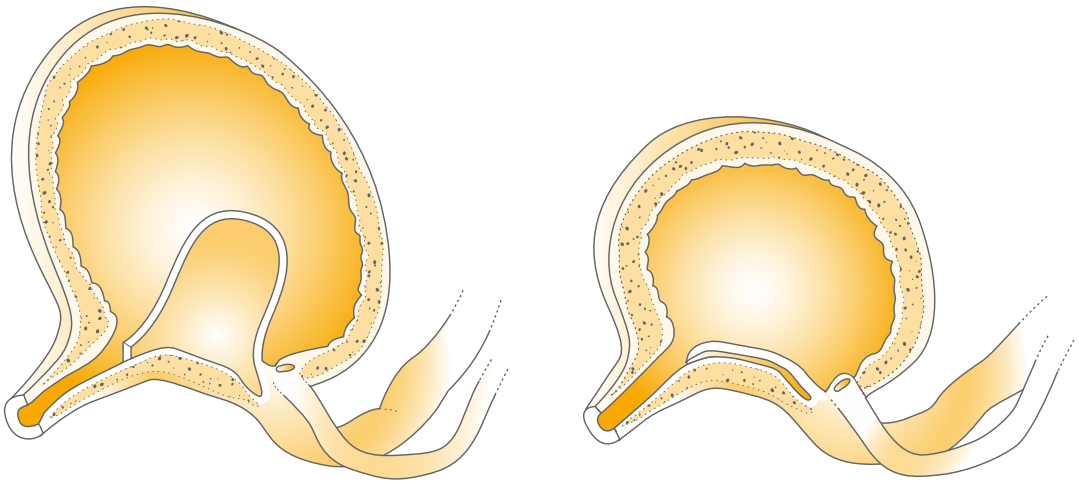


FIGURE 40.10 Sphincteric variant of extravesical ureterocele subtending upper-pole ureter of a duplex system. The orifice opens proximal to the external sphincter. Normal contraction of the bladder neck may contribute to ureteral obstruction.

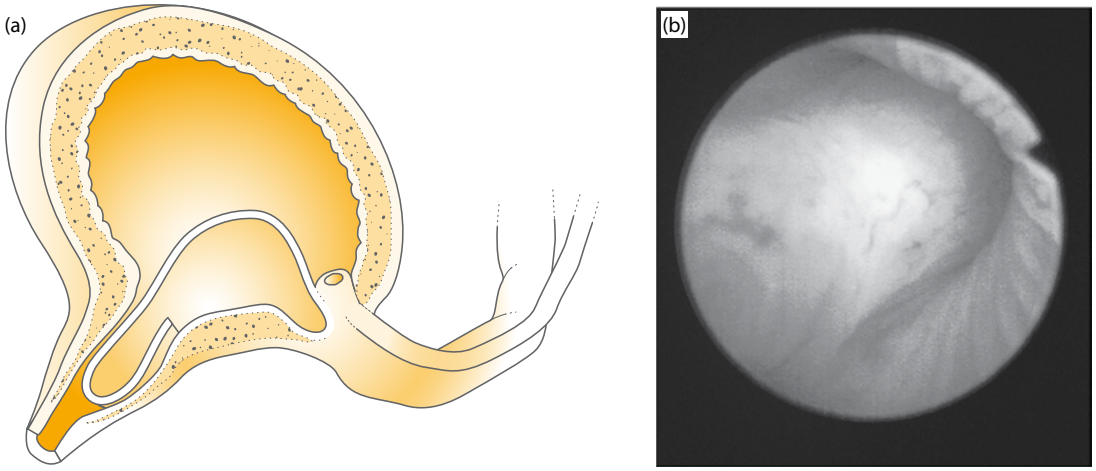


FIGURE 40.11 (a) Cecoureterocele variant of an extravesical ureterocele. Blind-ending extension beneath submucosa of the urethra can prolapse and/or cause bladder outlet obstruction. (b) Cystoscopic appearance of urethral extension of cecoureterocele.

Characteristics

Ureteral Duplications

Duplication is the *most common congenital anomaly in the urinary tract*: a *0.7% incidence* was found in one series of more than 50,000 autopsies.[32] Intravenous urograms demonstrate duplications in 4% of studies, and hydronephrosis and scarring are seen in 27% of these.[33] Females are affected two to four times more commonly than males. The right and left collecting systems are affected equally. Bilateral duplications occur in 17%–33% of cases. The anomaly is an inheritable defect transmitted in an autosomal fashion having variable penetrance.[34] The parents or siblings of a child with a duplex ureter have as much as a one in eight chance of having a similarly affected child.[35]

Ectopic Ureters

The incidence of ureteral ectopia was approximately 1 in 2000 in one series of autopsies in children. Many remain asymptomatic, and a true incidence is difficult to determine.[36]

Ectopic ureters occur in *females two to three times more commonly* than in males,[1,2,37] although as high as 12-fold increases have been cited.[38] *More than 80% of females with ectopic ureters have duplex systems. The majority (75%) in males are singlets.*[39,40] Between *70% and 80%* of ectopic ureters are associated with *complete duplications*. Nearly 20% of patients with ureteral ectopy have bilateral involvement.[37] In one report of nearly 500 ectopic ureters, the posterior urethra and prostatic urethra (57%) were the most common sites of drainage in males. The seminal vesicle (33%) was also commonly involved. More remote terminations at the ejaculatory duct and vas were rare (10%). The urethra and vestibule were the most common drainage sites for 69% of females. Vaginal ectopy occurred in another 25%.[37]

Ureteroceles

The incidence of ureteroceles was as high as 1 in 500 in one autopsy study.

They occur in *females four to six times more commonly* than in males.[41–43] Ureteroceles in girls are associated with

duplex systems 95% of the time. By contrast, up to 66% of boys have single-system anomalies.[44] Nearly all appear in Caucasians.

Eighty percent of ureteroceles are associated with the upper pole of a duplex system. The remainder are single-system ureteroceles. Bilateral involvement occurs in 15% of cases.[45,46] A genetic predisposition has been shown,[47] but familial cases are rare.[48] The anomaly is more commonly seen in Caucasians than in other races.[43]

CLINICAL PRESENTATION

Antenatal ultrasonography has dramatically increased the detection of urinary anomalies and, in some cases, has altered our understanding of their natural history. The yield from routine screening is significant. Abnormalities of the urinary system are detected in approximately 1 in 500 studies, second only to those of the nervous system. The breakdown of diagnoses in a typical series is shown in Table 40.2. Notably, ectopic ureters, duplications, and ureteroceles can all be detected prenatally. Further evaluation after birth is warranted, even in instances where the anomaly was present earlier in gestation and has presumably resolved.[49] In many cases, the exact etiology of hydronephrosis, the most common finding, cannot be determined until after delivery. Prenatal cases of bladder outlet obstruction have been reported.[50] Antenatal intervention has been described for rare cases of bladder outlet obstruction caused by ureteroceles.[51,52] Such cases are exceptional, and intervention is unlikely to provide much benefit. Because of the tendency for urinary infections to occur with hydronephrosis, it seems reasonable to keep newborns on prophylactic antibiotics (amoxicillin, for example) until their anatomy is better defined (see the "Evaluation and Diagnosis" section below).

After delivery, an *extravesical ureterocele represents the most common cause of bladder outlet obstruction in newborn girls and the second most common cause in boys, after posterior urethral valves* (PUVs). A true pediatric urologic emergency can result, depending on the degree of obstruction. The diagnosis of an obstructing ureterocele should be considered in any infant, especially a girl, with bladder distension, anuria, or ascites.[53] When full-blown prolapse occurs, clinicians will encounter a congested, ecchymotic interlabial mass (Figures 40.12 through 40.15). The mass may have varying hues, depending on the degree of vascular compromise. Since prolapse usually occurs down the posterior wall of the urethra, the meatus will be evident anteriorly and can be catheterized. Cecoureteroceles, the distal projections of which extend down the urethra, have a less protuberant appearance if they reach the perineum. They are rarely ecchymotic since vascular compromise is not an issue (Figure 40.16). The smooth wall of the ureterocele helps differentiate it from the more ominous grapelike sarcoma botryoides. The white mucus-filled periurethral (Skene's) duct cyst is considered in the differential, as is Gartner's duct cyst. The latter can protrude from the vagina and become

TABLE 40.2 Prenatal diagnosis of hydronephrosis and the breakdown of prenatally diagnosed duplex systems

Prenatal diagnosis of hydronephrosis (177 cases)[a]	
Hydronephrosis:	154
Bilateral hydronephrosis	73
Unilateral hydronephrosis	61
Bladder outlet obstruction	9
Duplex/hydronephrosis	9
Prune belly syndrome	2
Multicystic dysplastic kidney	10
Autosomal recessive kidney	5
Other	8
Breakdown of prenatally diagnosed duplex systems (39 cases)[b]	
Ureterocele	15
Ectopic ureter	15
Lower pole reflux	6
Lower pole UPJ obstruction	2
Yo-yo reflux	1

[a] Adapted from Mandell J et al. *Radiology* 1991;178:194.
[b] Adapted from Jee LD et al. *J Urol* 1993;149:808–10.

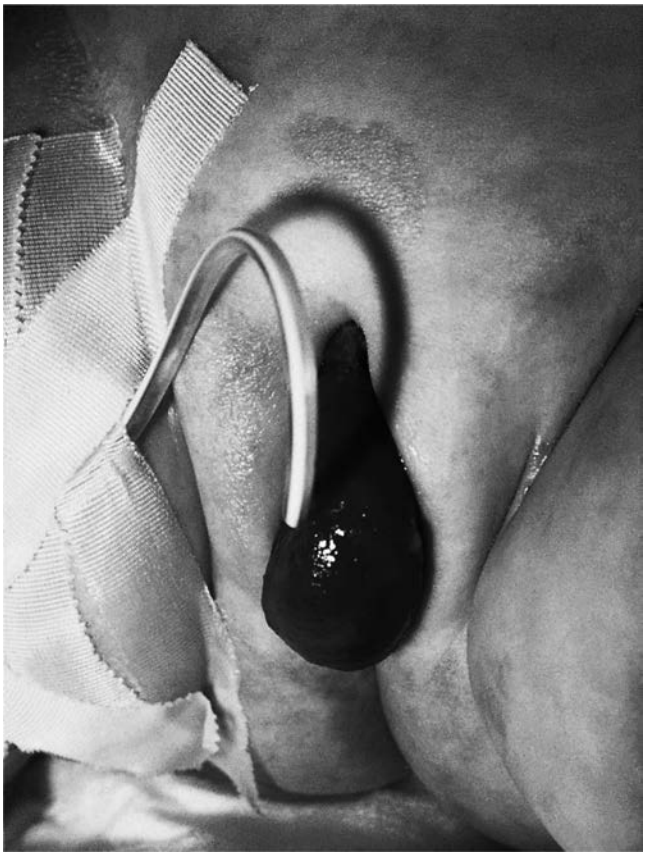


FIGURE 40.12 Congested and ecchymotic prolapsed ureterocele presenting as an interlabial mass.

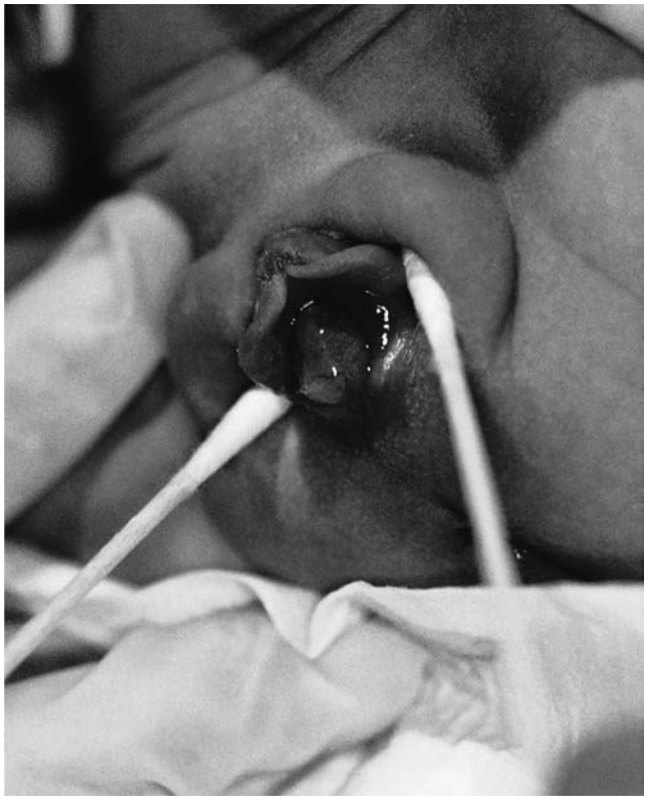


FIGURE 40.13 After incision at bedside, the ureterocele is decompressed and retracts into the bladder after a few days. Given the severity of this type of defect, lower urinary tract reconstruction is ultimately warranted in affected infants.

FIGURE 40.14 Prolapsing ureterocele associated with nonfunctioning upper-pole moiety appears as a filling defect occluding the urethra on EU.

infected. It is often associated with an ectopic ureter that is blind ending at its proximal extent or connected to a rudimentary kidney.[54,55] When not evident on examination, the diagnosis of an obstructing ureterocele (or other urethral obstruction) is suggested by the history of a weak or intermittent stream.

More commonly, ureteroceles cause unilateral hydronephrosis from ureteral blockage. In severe cases, an abdominal mass becomes palpable. Patients not detected antenatally typically present with UTIs (Figures 40.17 and 40.18). Duplication anomalies were detected in 63 (8%) of 774 children evaluated for an initial UTI during the first 6 years of life.[56] In another series of 58 ureteroceles, 90% were identified before age 3, half of whom presented with UTIs.[15] Nonspecific symptoms of failure to thrive and colic also occur.

Flank pain, fever, and abdominal mass are common presentations of ectopic ureters left undetected until a later age.[57] Urine cultures can be negative when the infected ectopic system is not draining into the bladder. Intermittent vaginal discharge is sometimes seen. A high index of suspicion is warranted. Ureteroceles can cause irritative voiding symptoms secondary to obstruction or infection, but voiding abnormalities accompany ectopic ureters far more commonly. In addition, the distal segment of ectopic ureters inserting at the verumontanum can elevate the bladder neck, causing outlet obstruction in boys of any age.[58] It is important to remember that *ectopic ureters always insert proximal to the urinary sphincter in males*. As a result, incontinence does not usually occur in boys with the anomaly. Bilateral single ectopic ureters, associated with bladder neck maldevelopment and lack of sphincter control, are one exception (see below). Another is the frequency and urgency that sometimes results from the trickle of urine into the posterior urethra.[37] However, the more usual proximal insertions into structures of Wolffian origin (seminal vesical, vas, and epididymis) present their own problems for affected boys. Ureteral ectopia should be suspected in any infant or child who presents with a culture-proven case of epididymo-orchitis.

Clinicians should be wary of any girl who reportedly has never been fully toilet trained. These patients must be approached with an open mind, and the possibility of an ectopic ureter always entertained, especially when damp underwear is found on examination. In many cases, a cadre of physicians have treated the patient for presumed bladder dysfunction or psychosocial problems, including sexual abuse.[59] When the ureter exits along the urethra, the voiding pattern often includes seemingly normal bladder control and spontaneous emptying (from the other ureters having normal bladder insertion), followed by an uncontrollable loss of urine as the obstructed system vents secondarily (Figure 40.19). With vaginal ectopy,

FIGURE 40.15 Large ureterocele associated with nonfunctioning right kidney occluding the bladder and contralateral kidney. Given its size and position, prolapse through the female urethra of such a variant, especially with urethral extension, is easy to envision.

continuous wetting in a girl having an otherwise normal micturition pattern and control (in contrast to bladder dysfunction) is a classic presentation (Figures 40.20 and 40.21).[60] The degree of incontinence depends on the urinary output from the affected kidney. In occasional cases where small amounts of urine are produced, sporadic incontinence occurs only while standing. The latter is commonly mistaken for vaginal voiding or stress incontinence. Table 40.3 summarizes the clinical manifestations of these two ureteral anomalies.

Both anomalies sometimes remain undetected until adulthood.[61,62] Ectopic ureters in girls that pass through the urinary sphincter but are positioned proximal to the meatus can maintain continence during development. Multiparity can unmask the anomaly, which is often mistaken for stress incontinence. With cases of ectopic ureters that terminate in the male genital tract, prostatitis, seminal vesiculitis, and epididymitis can all occur. Most do not become apparent until the onset of sexual activity. Historically, single-system ureteroceles usually presented during adulthood. An intravesical location coupled with preserved renal function allowed most to go unnoticed until later age (Figure 40.22). This accounted for their prior designation as "adult type," a label since dropped with the advent of antenatal diagnosis. Common presentations still include urinary calculi, milk of calcium, and recurrent UTIs.[63]

EVALUATION AND DIAGNOSIS

Ectopic ureters and ureteroceles present diagnostic dilemmas when it is difficult to determine from which renal moiety they arise. They can also mimic one another at the bladder level, which has implications for treatment.

A sonogram (also called ultrasonography, ultrasound, or US) and voiding cystourethrography (VCUG) are indicated in the initial evaluation of any child suspected of having a ureteral anomaly. Once detected, a functional test (radionuclide renal scan) becomes necessary to the decision-making process when considering the different

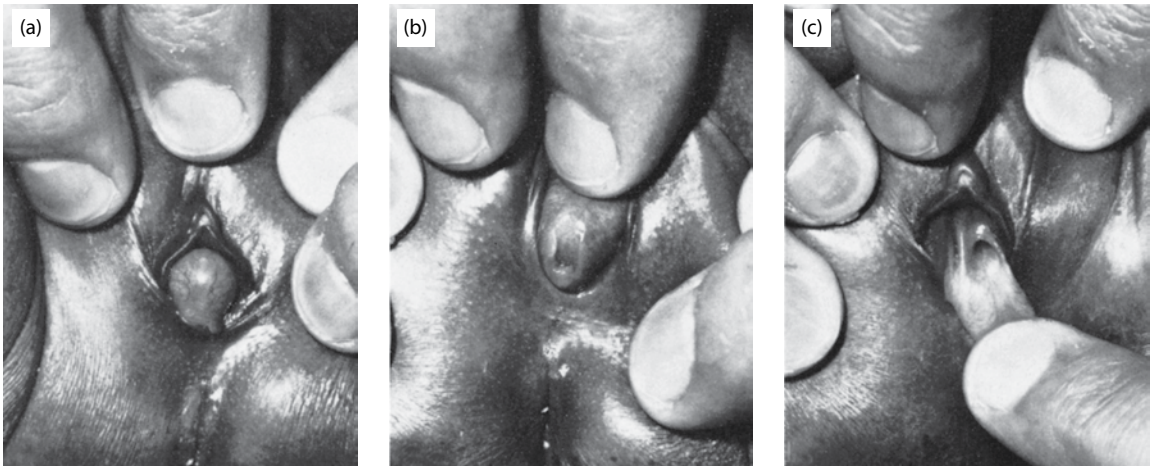


FIGURE 40.16 (a) Typical presentation of a cecoureterocele. (b) The cecoureterocele is pushed upward, revealing the hymenal ring below. (c) The urethra can be seen above the ureterocele. This ureterocele has a more natural pink coloration, distinguishing it from a periurethral skene's duct cyst, which is yellow and mucus filled.

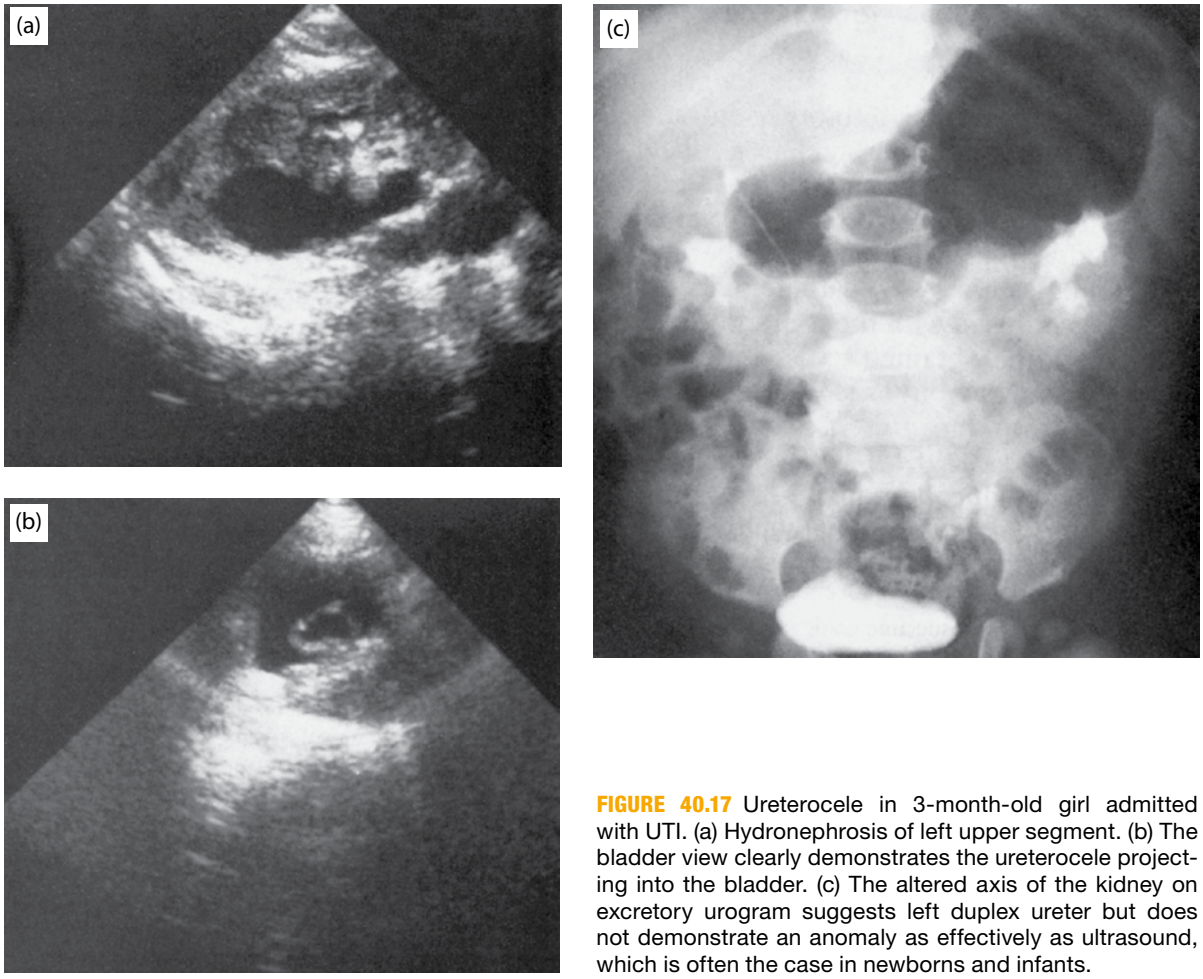


FIGURE 40.17 Ureterocele in 3-month-old girl admitted with UTI. (a) Hydronephrosis of left upper segment. (b) The bladder view clearly demonstrates the ureterocele projecting into the bladder. (c) The altered axis of the kidney on excretory urogram suggests left duplex ureter but does not demonstrate an anomaly as effectively as ultrasound, which is often the case in newborns and infants.

options in management. Additional studies—e.g., excretory urography (EU), computerized tomography (CT), or magnetic resonance urography (MRU)—are also sometimes necessary. Cystoscopy, sometimes in concert with retrograde ureteropyelography (RUP), completes the evaluation.

Ultrasonography

During initial screening, the differentiation of single from duplex systems is usually made possible by ultrasound evaluation. *The renal manifestations of ureteroceles and ectopic ureters can be identical*. Variable degrees of hydronephrosis of the affected kidney or upper-pole moiety depend on the severity of ureteral obstruction (Figure 40.23). Hyperechoic parenchyma is suggestive of dysplasia. With duplication, the adjacent lower pole can also be hydronephrotic. Reflux (because of lateral ectopia) or obstruction caused by the dilated upper-pole ureter must be considered. Hydronephrosis of the lower-pole moiety and contralateral kidney can also result from bladder outlet obstruction or direct compression by ureterocele.

Ultrasonography should always include a survey of the bladder, where the two anomalies can often be differentiated. Ultrasound is probably the best study for making the diagnosis of ureteroceles, which usually appear as thin-walled cystic protrusions from the posterolateral side of the bladder (Figure 40.24). The ureter can then be followed deep within the bony pelvis and, in some cases, up to the kidney.[64,65] The degree of bladder fullness, however, can reduce the sensitivity of the study. Overdistension causes some ureteroceles to collapse, whereas an empty bladder can allow a large ureterocele to completely fill the bladder. This gives the impression of a partially full but normal bladder. Ectopic ureters will sometimes displace the bladder and mimic a ureterocele, resulting in a so-called *pseudoureterocele* (Figures 40.25 and 40.26).[66] The muscle wall of the bladder gives a thicker line of demarcation between its lumen and that of an ectopic ureter than the thin wall of a ureterocele. More typically, the dilated ectopic ureter will taper and terminate into an abnormally inferior position beneath the bladder base. Occasionally, the ureter associated with either anomaly is so tortuous and dilated that it mimics a cystic abdominal mass with multiple septae.

In occasional cases, these ureteral abnormalities result in dilatation of the renal moieties they subserve. More typically, the kidneys associated with single-system anomalies are sometimes small and abnormally positioned, making them difficult to localize (ureterocele disproportion) (Figure 40.27).[67] In similar fashion, the upper-pole variants accompanying duplex variants can be tiny dysplastic

FIGURE 40.18 Gross pus from vagina of infant with ectopic ureter.

remnants crowning otherwise normal kidneys. In both instances, a dilated ureter or ureterocele is still often visualized at the level of the bladder. Additional diagnostics become necessary to define the anatomy more fully.

Voiding Cystourethrography

The voiding cystourethrogram provides the most definitive assessment of the bladder, urethra, and in some cases, distal ureters. Infant feeding tubes are used to perform this test. These allow for spontaneous voiding and avoid any confusion or distortion offered by the balloons of Foley catheters. Ureteroceles appear as smooth, broad-based filling defects positioned near the trigone. Some ureteroceles evert into the ureter with the bladder full and appear as a diverticulum.[68] This is especially true of single-system ureteroceles, where mimics of periureteral diverticula were seen in nearly one-half of VCUG in one series.[69] Other ureteroceles efface during the latter stages of bladder filling and cannot be appreciated. Obtaining images early during the filling phase aids in detection before contrast can obscure the ureterocele. An eccentric position may help define the involved side, although many ureteroceles appear centrally located. When laterality cannot be determined and cystoscopy is inconclusive, a cyst puncture with retrograde injection may become necessary.

The presence of VUR plays an important role in the management of ureteroceles. Reflux can occur into the ipsilateral lower pole, since the backing required of an effective flap valve is presumably lost with the posteriorly positioned ureterocele (Figure 40.28). Lateral ectopia, trigonal distortion, and eversion of the ureterocele can also contribute and become important factors in the planning of subsequent management. At times, the ipsilateral reflux is severe enough that the ureterocele and its duplex kidney are not detected until the time of surgery.[70] Reflux is also seen in the contralateral system if the anomaly is large enough to distort the trigone and opposing submucosal ureteral tunnel. In one series of 148 ureteroceles, ipsilateral VUR was seen in 80 (54%), whereas contralateral reflux was appreciated in 28%.[71] Smaller series have documented similar incidences.[72,73] Reflux into the ureterocele itself is uncommon but can also occur (Figure 40.29).

VUR is also a common finding with ectopic ureters (Figure 40.30). The ipsilateral lower-pole ureter refluxes in at least 50% of cases. Upper-pole VUR can also be appreciated, depending on the position of the ectopic orifice. Ectopic ureters whose distal extent is positioned within the bladder neck can both reflux and obstruct. Obstruction is intermittent, and emptying occurs during voiding, in concert with relaxation of the surrounding musculature. Reflux occurs once the ureter is somewhat emptied. This phenomenon may only be appreciated by *performing cyclic (repeated) voiding studies*.[74] Orifices proximal to the bladder neck freely reflux with or without voiding.

Excretory Urography

Despite its declining role in the routine evaluation of children with urinary tract problems, EU sometimes remains a useful tool in the workup of certain ureteral anomalies (Figures 40.31 and 40.32). This is occasionally the case with ureteroceles, when the anatomy is indefinable with ultrasound and renal scintigraphy alone, and is more often true with ectopic ureters. For girls with infrasphincteric ectopia, who arrive with the classic history of constant urinary dribbling despite being successfully toilet trained, EU is often the only imaging study necessary to make the diagnosis (Figures 40.33 and 40.34).[75] Radiographic signs of the nonfunctioning, occult duplications found with ectopic ureters are shown in Table 40.4.

Ureteroceles with minimally functioning upper-pole moieties can cause identical upper tract findings. The ureterocele appears as a filling defect within the bladder that gradually fills with contrast from the other functioning kidney. When ureteroceles are associated with a functioning kidney, they appear as a contrast-filled "cobra head" at the ureterovesical junction.

Renal Scintigraphy

Radionuclide scans help to quantify the amount of functioning renal parenchyma. This is crucial information when renal salvage is being considered. The degree of

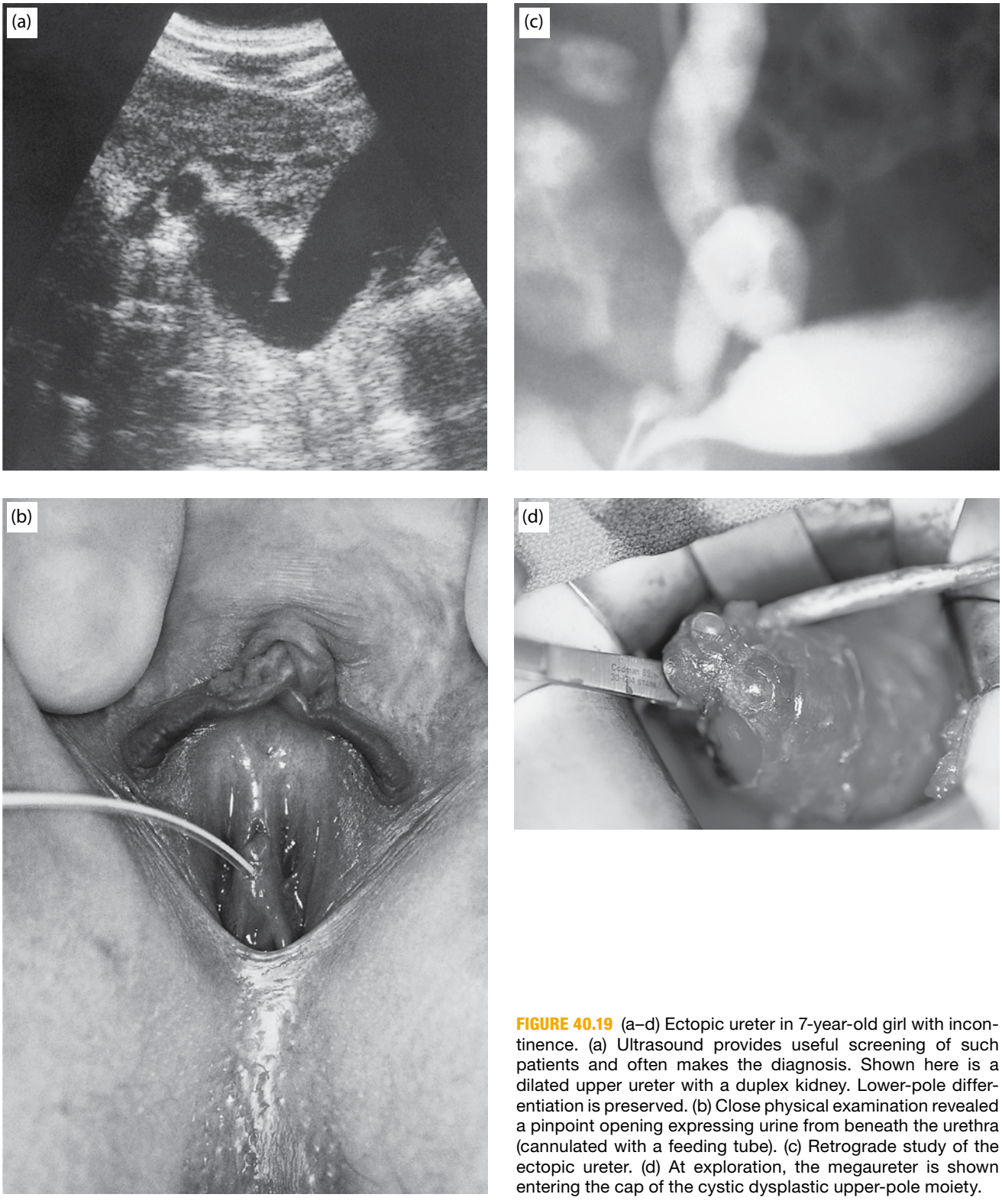


FIGURE 40.19 (a–d) Ectopic ureter in 7-year-old girl with incontinence. (a) Ultrasound provides useful screening of such patients and often makes the diagnosis. Shown here is a dilated upper ureter with a duplex kidney. Lower-pole differentiation is preserved. (b) Close physical examination revealed a pinpoint opening expressing urine from beneath the urethra (cannulated with a feeding tube). (c) Retrograde study of the ectopic ureter. (d) At exploration, the megaureter is shown entering the cap of the cystic dysplastic upper-pole moiety.

obstruction is also assessed, although most ectopic ureters and ureteroceles, by default, exhibit delayed drainage because of ureteral dilatation. Technetium 99m (^{99m}Tc) diethylenetriamine pentaacetic acid (DTPA) and mercaptoacetyltriglycine (MAG3) scans provide reasonable assessments of function and obstruction. Since ^{99m}Tc dimercaptosuccinic acid (DMSA) scans result in renal tubular labeling and are unaffected by obstruction, they are more sensitive to low levels of renal function and are sometimes helpful in detecting occult duplex anomalies and small kidneys associated with ureteral anomalies that are not identified by other techniques.[76,77] It provides the gold standard in assessment of renal function. DMSA scintigraphy can also detect subclinical cortical defects and

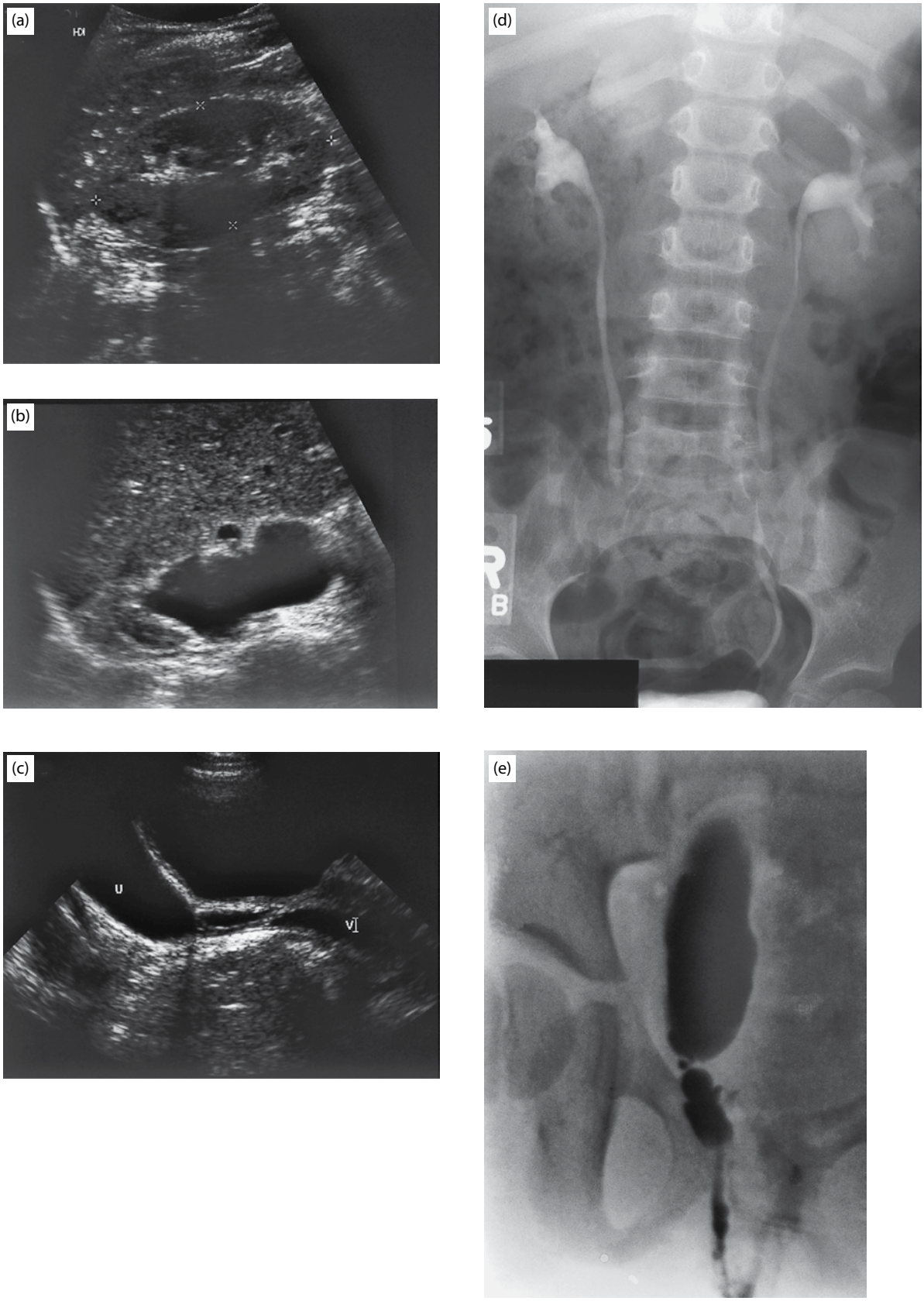


FIGURE 40.20 Urinary incontinence in a teenage girl felt to have bladder dysfunction. (a) Some views of the right kidney by ultrasound look fairly benign. (b) More proximal views are revealing and show a superiorly positioned cystic mass. (c) Pelvic views demonstrate the ureter entering the vagina. (d) EU shows the duplicated right kidney, with evidence of function of the upper pole. (e) Retrograde study of the ectopic ureter.

TABLE 40.3 Clinical presentations
Ectopic ureters
Both Sexes
Acute or recurrent urinary infection
Abdominal mass/pain
Failure to thrive
Females
Continuous dampness with otherwise normal voiding pattern after toilet training
Vaginal discharge
Orifice evident along the urethrovaginal septum
Males
Epididymo-orchitis
Urgency and frequency
Constipation, pelvic pain, painful ejaculation, epididymitis
Ureteroceles
Both Sexes
Acute or recurrent UTIs
Hematuria
Failure to thrive, abdominal or pelvic pain
Abdominal mass
Females
Prolapsed interlabial mass
Bladder outlet obstruction
Males
Bladder outlet obstruction

functional impairment in lower-pole moieties that show no ultrasonic evidence of parenchymal damage.[78]

Some clinicians believe that the transitional physiology of the newborn may affect the perinatal kidney's handling of radionuclides and contrast. This could contribute to the lower yield of functioning kidneys in historical series when EU was obtained in newborns and provided the usual measure of function. It could also result in overestimates of the recovery of function after procedures done to alleviate obstructed newborn kidneys, when early scans are compared with studies performed when the physiology is more conducive to scanning. As a consequence, scans performed early after delivery may not provide an accurate assessment of renal function and should probably be deferred for 4–6 weeks after delivery to allow for some maturation of renal function.

Magnetic Resonance Imaging

MRU is becoming increasingly useful in cases where conventional imaging studies fail to delineate occult dysplastic renal moieties, ectopic ureters, and ureteroceles.[79,80] Respiratory-gated excretory and static fluid MRUs appear to complement each other well in evaluating such systems.[81] In one study of 55 patients, virtual magnetic resonance was compared with cystoscopy and

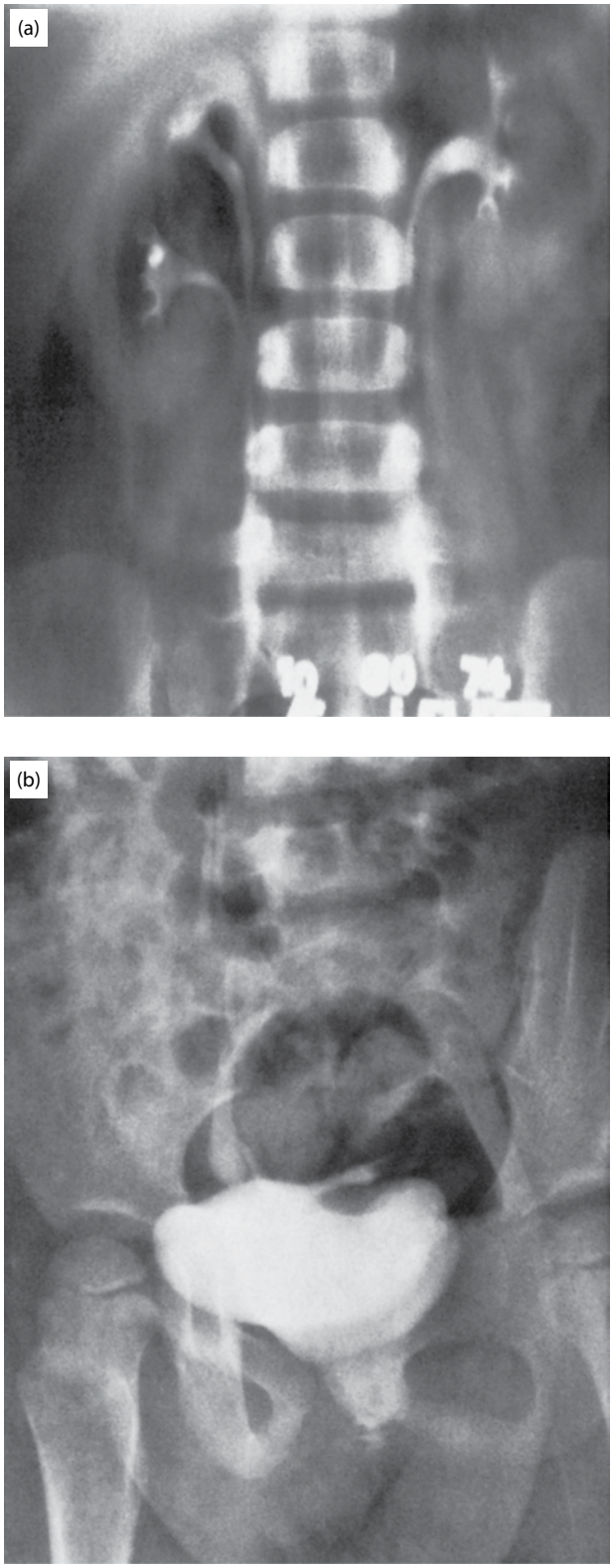


FIGURE 40.21 Ectopic ureter in a 4-year-old girl with incontinence, demonstrated by excretory urograms. (a) Duplication on the right. (b) Pooling of medium into the vagina from the ectopic ureter.

FIGURE 40.22 Single-system intravesical ureterocele presenting as UTI in a 16-year-old. If the impressive dilatation above a small ureterocele represents a progressive change, questions are raised about the natural history of the anomaly and the validity of expectant treament of antenatally diagnosed ureteroceles.

other diagnostic modalities, including ultrasonography. It was found to be the most sensitive modality in assessing concurrent genitourinary abnormalities. The modality allowed uniquely better definition of ureterocele anatomy and the insertions of ureters felt to be possibly ectopic.[82,83] Others have confirmed these findings.[84] Contrast-enhanced T1-weighted sequencing provides a contemporary alternative to intravenous urography. The T2-weighted sequences provided unenhanced static-water views and assessment of the adjacent soft tissue. Taken together with three-dimensional reconstruction, MRU offers an extremely sensitive and attractive alternative to any other option in diagnostic assessment. Availability, expense, and the need for sedation are detriments to its widespread usage, and at present, the study is utilized for cases where complex anatomy cannot be defined with other modalities.

Other Diagnostic Modalities

CT scans are sometimes helpful in defining the anatomy of kidneys with collecting systems of bizarre appearance. Duplications in which both ureters and renal pelves are dilated are one example. CT can also be considered for patients suspected of having ureteral ectopia or ureterocele disproportion but whose poorly functioning renal moiety cannot be defined by other modalities (Figure 40.35).[85–87]

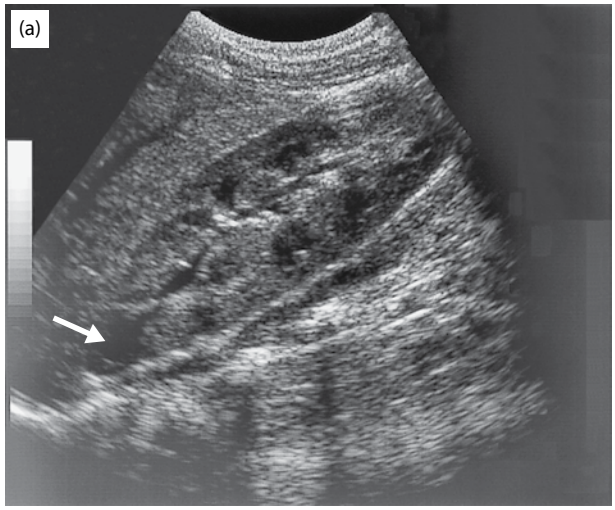
Percutaneous drainage can also be used to vent obstructed kidneys or renal segments that appear salvageable by ultrasound but function poorly. However, recoverability of function is rare when renal scintigraphy demonstrates little function.

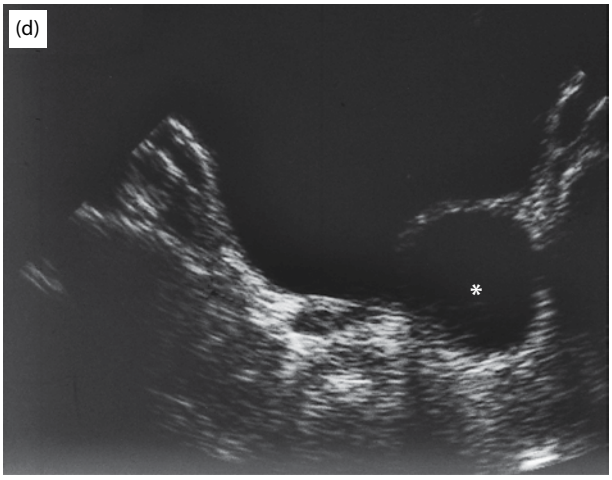
A variety of *dye tests* have been used to clinically diagnosis ectopic ureters. For example, indigo carmine or methylene blue can be instilled in the bladder with a catheter, which is then removed. Continued evidence of dampness and leakage of clear urine implicates ureteral ectopia. Another test involves placing a dental roll in the vagina. After indigo carmine is given intravenously, the roll will appear blue, provided that there is some function to the affected kidney and the child has not stained the roll by spontaneously voiding. The relative invasiveness of such tests, coupled with the increased sensitivities of today's diagnostics, has reduced their utility in most cases.

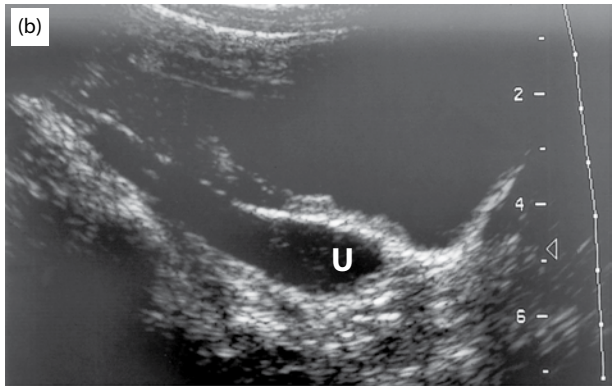
Cystoscopy

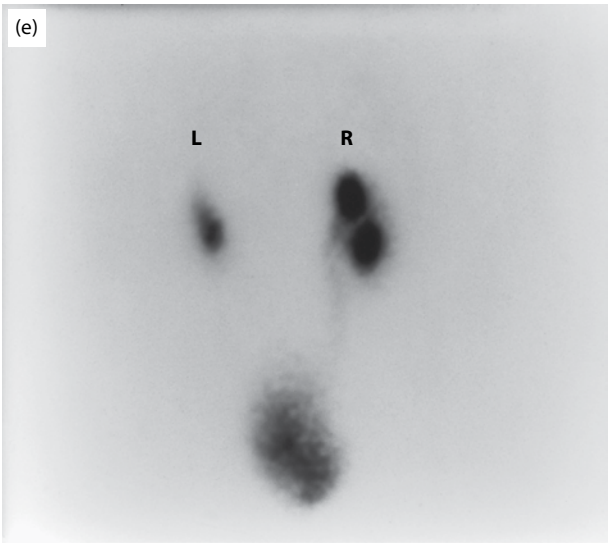
Examples of the cystoscopic appearance of ureteroceles are shown in Figure 40.47. With smaller *intravesical ureteroceles*, the cystic dilatation expands with each peristalsis and then shrinks as urine drains through its orifice. Not all variants are as easy to appreciate, however, and appearances can change with bladder filling. Starting with the bladder empty and examining with the slow filling of irrigant is helpful. *Extravesical variants* have ill-defined borders that can undermine the bladder neck and urethra. If the bladder is overfilled, they efface and can even appear to be a diverticulum. The orifice of the ureterocele may be difficult to appreciate but is often positioned distal to the bladder neck and, with cecoureterocele and sphincteric variants, will balloon open with the efflux of irrigant. With larger ureteroceles, the adjacent ureteral orifices are also difficult to appreciate because of displacement.

Cystoscopy is less helpful for ectopic ureters. The ectopic orifice cannot be appreciated in more than half of cases. Bladder neck and urethral ectopy offer a high yield. Prostatic ectopy sometimes presents as a widened ejaculatory duct that allows easy retrograde study.[39] Examining the vaginal vault along its anterior or lateral aspect for GYN-ectopy is less fruitful. In rare cases, a small cystic structure is identified that can be unroofed and cannulated for retrograde study.[31] Intravenous indigo carmine is sometimes excreted by even minimally functioning









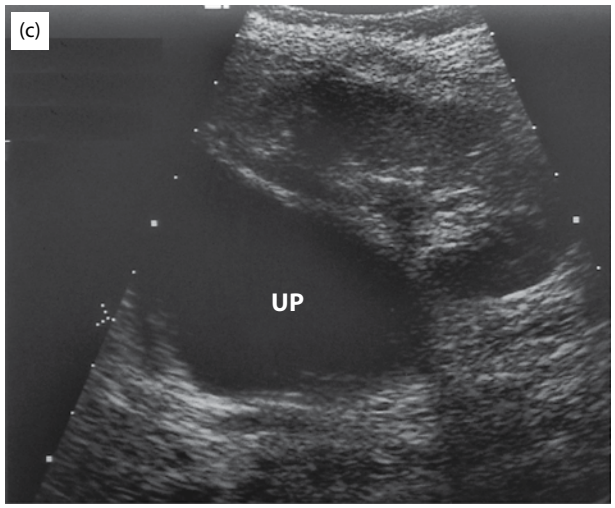


FIGURE 40.23 Variable appearance of hydronephrosis with duplications. (a) Subtle suggestion of obstructed duplication (arrow) of the upper pole in a 10-year-old girl with persistent urinary incontinence. (b) Dilated ureter shown behind the bladder (U). Urethral ectopy was found as the cause of wetness. (c) Second adolescent girl with similar presentation and vaginal ureteral ectopy. Ultrasound shows markedly dilated upper-pole (UP) moiety of the left kidney. (d) A transverse view of the bladder shows impingement by a dilated ureter and a pseudoureterocele appearance (*). (e) Renal scintigraphy shows a deviated axis of the left lower pole and no function of the upper pole.

kidneys and can aid in identification. Within the bladder, the hemitrigone on the affected side is often underdeveloped and may be elevated from behind by the dilated ureter. In some cases, the dilated ureter can be palpated on rectal examination. Failure to identify the ectopic orifice rarely changes management. In cases where a lower tract approach is planned, the ectopic ureter can be identified outside the bladder or transvesically after incising the trigone on the affected side (see the next section, "Management Considerations").

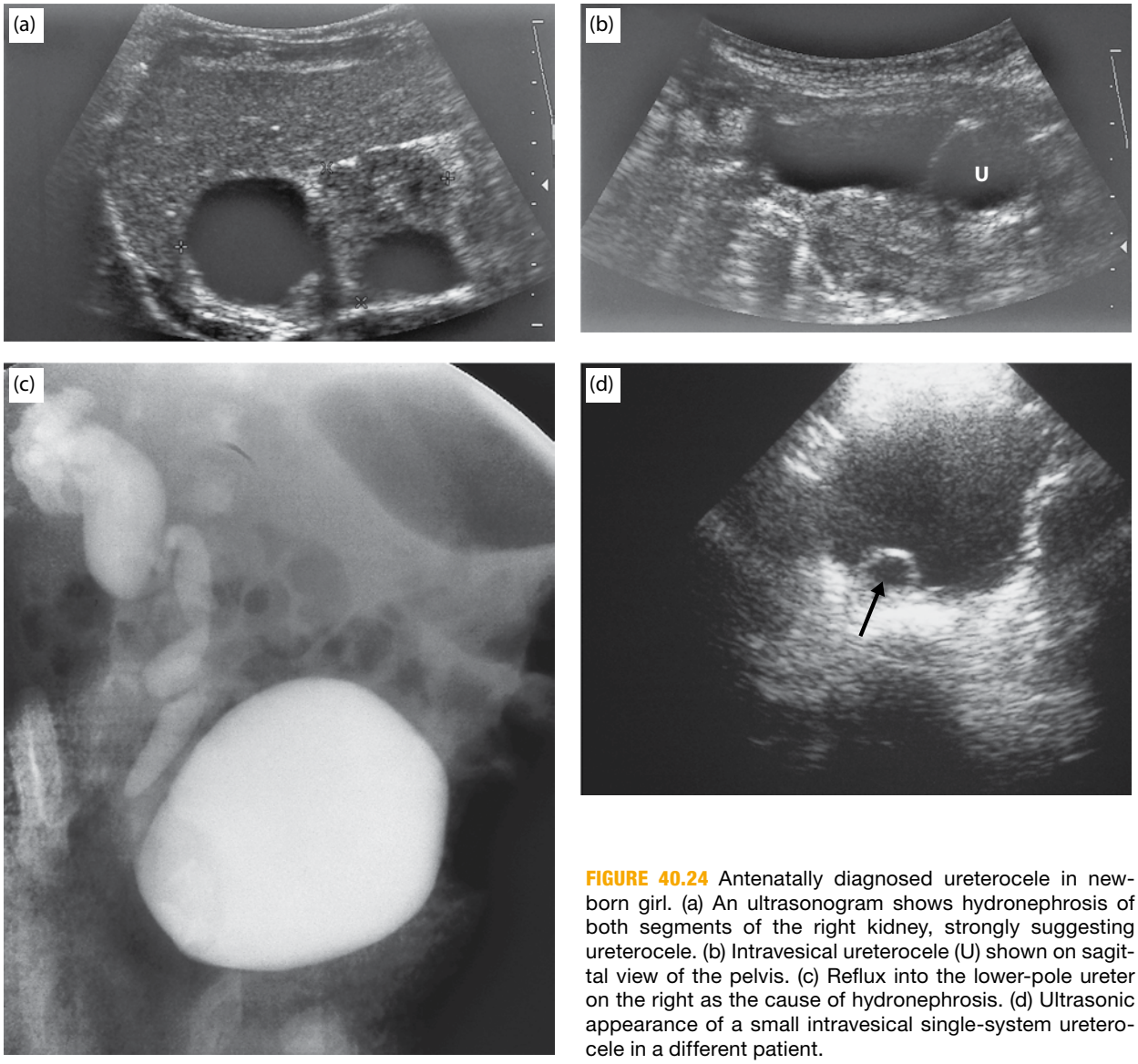


FIGURE 40.24 Antenatally diagnosed ureterocele in newborn girl. (a) An ultrasonogram shows hydronephrosis of both segments of the right kidney, strongly suggesting ureterocele. (b) Intravesical ureterocele (U) shown on sagittal view of the pelvis. (c) Reflux into the lower-pole ureter on the right as the cause of hydronephrosis. (d) Ultrasonic appearance of a small intravesical single-system ureterocele in a different patient.

MANAGEMENT CONSIDERATIONS

Once the workup is complete and the diagnosis made, the management of ectopic ureters and ureteroceles is defined by the answers to the following questions:

1. Is the affected ureter a singlet or a portion of a duplex system?
2. Is the affected ureter obstructed, refluxing, or both?
3. Are the contralateral and/or ipsilateral ureters and/or the bladder affected by the primary anomaly?
4. What is the status of the kidney or portion of kidney associated with the ureter in question?
5. What is the age and clinical status of the patient?

A description of the experience with various techniques and their technical nuances follows. Simply put, the algorithms in the management of these two anomalies historically branched with two main decisions: whether to save or discard the involved kidney and whether there is a need to reconstruct the bladder. These remain the mainstays of management for *ectopic ureters*.

The recommendations for *ureteroceles* have become controversial, however, with the inclusion in the treatment armamentarium of selective puncture. A minimally invasive and a seemingly simple solution, the benefits of cystoscopically decompressing ureteroceles must be weighed against the risks of creating reflux in the involved ureter.

Until recently, the *two main areas of contention with ureteroceles* dealt with the salvage of functioning upper-pole moieties and the need, if any, for removal of ureteroceles subtending upper-pole segments after partial nephrectomy or proximal ureteral diversion (ureteroureterostomy or ureteropyelostomy) brought about their collapse (Figure 40.36). The introduction of selective

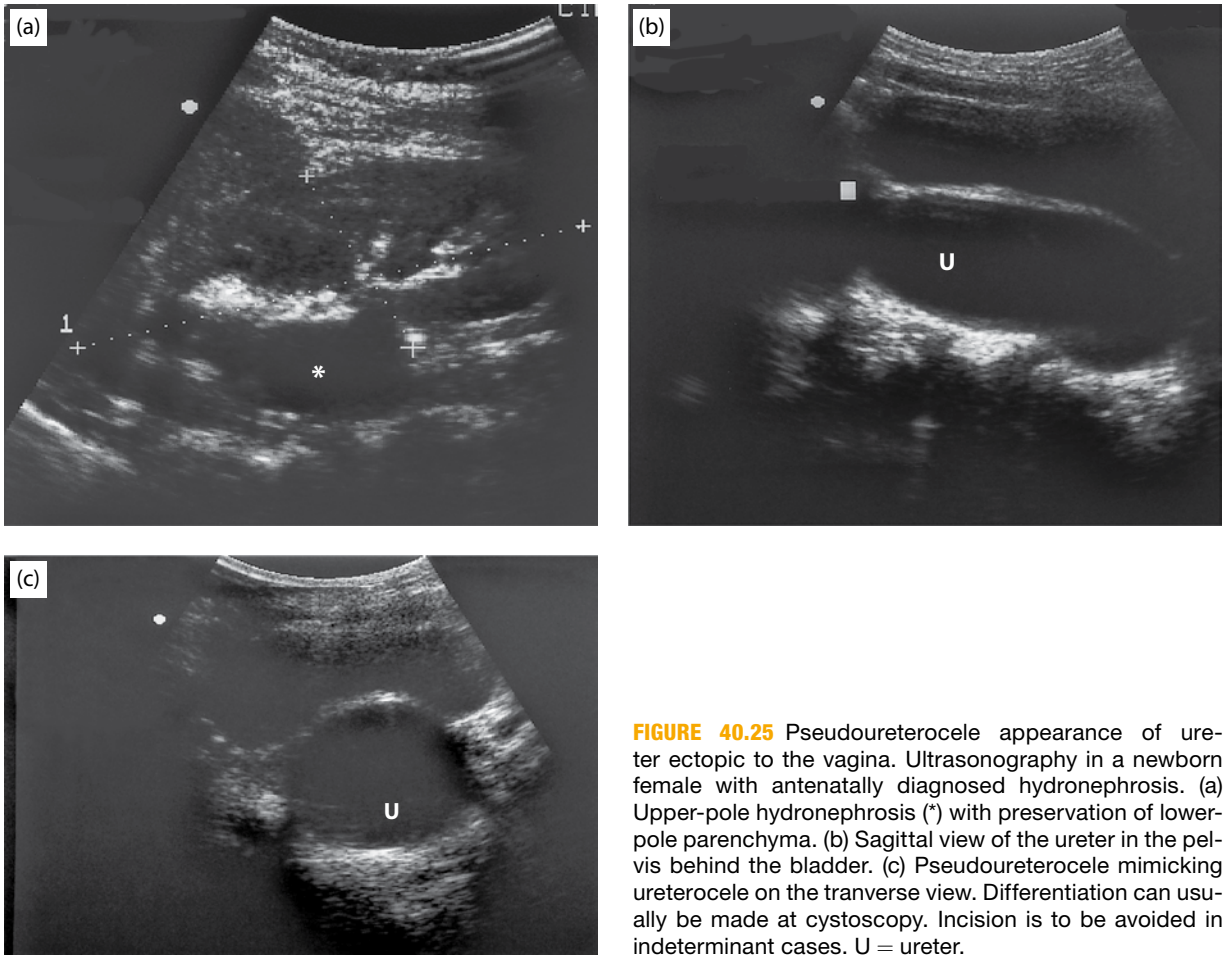


FIGURE 40.25 Pseudoureterocele appearance of ureter ectopic to the vagina. Ultrasonography in a newborn female with antenatally diagnosed hydronephrosis. (a) Upper-pole hydronephrosis (*) with preservation of lower-pole parenchyma. (b) Sagittal view of the ureter in the pelvis behind the bladder. (c) Pseudoureterocele mimicking ureterocele on the tranverse view. Differentiation can usually be made at cystoscopy. Incision is to be avoided in indeterminant cases. U = ureter.

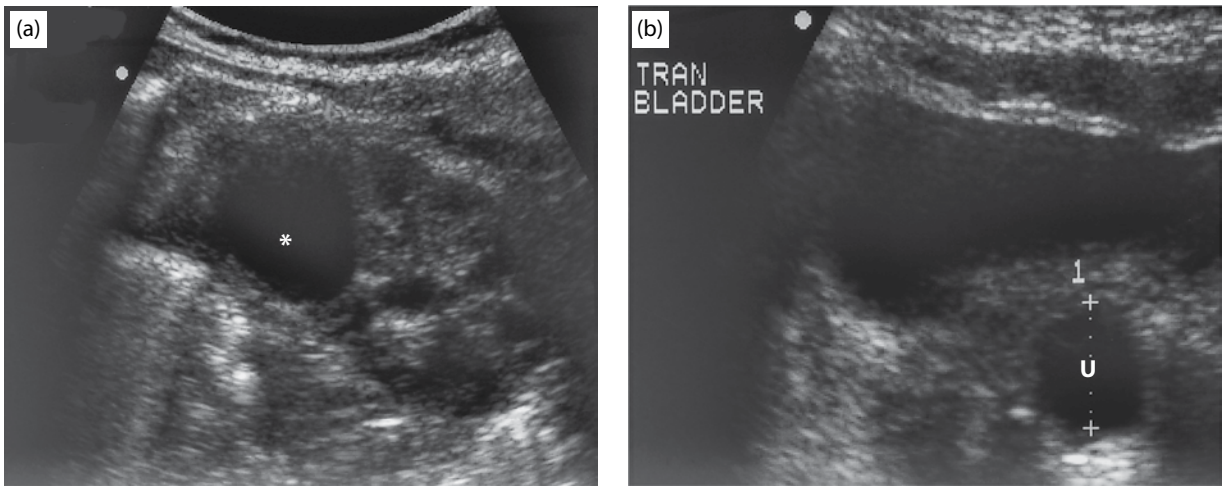


FIGURE 40.26 Ultrasonic evaluation of antenatally diagnosed hydronephrosis in a newborn girl. (a) Markedly hydronephrotic upper-pole moiety surrounded by virtually no parenchyma (*). (b) More typical appearance of ectopic ureter (U) en route to the vagina, where detrusor separating bladder lumen from the ureter is well developed.

puncture offers the obvious third controversy of which ureteroceles to decompress. The answers to these questions continue to be modified by contemporary clinical studies. A recent survey of pediatric urologists confirmed a considerable variation in management when offered typical clinical scenarios. Most practitioners reported seeing fewer than 10 cases per year, placing additional emphasis on the need for multi-institutional randomized controlled studies.[88]

A "cookbook approach" should be avoided when composing algorithms for the management of any urinary abnormality. The goals of therapy are generic to each

FIGURE 40.27 Gross example of ureterocele disproportion. Remnant dysplastic caps of tissue, as shown, are typically associated with massively dilated ureteroceles and ectopic ureters whose renal moiety cannot be appreciated diagnostically.

FIGURE 40.28 Massive reflux into the lower-pole ureter. An element of obstruction from the significantly enlarged ureterocele can also contribute to the dilatation.

patient: preservation of renal function and urinary continence with the elimination of obstruction, reflux, and infection. However, each patient requires individualized treatment, since there is often no uniform solution to every urologic anomaly. Nevertheless, trends become apparent in reviewing the literature that allow certain recommendations to be applied to most cases, which give the highest likelihood of a favorable outcome.

Recommendations for Management: Ectopic Ureters

Single System: Minimal or Nonfunctioning Kidney

Most kidneys (90%) that accompany single-system ectopic ureters do not function appreciably. Nephrectomy is the treatment of choice. In some cases, the question of renal salvage is raised by the appearance of marginal function on nuclear scintigraphy. *How much function is enough to warrant ureteral reconstruction rather than ablation of its associated kidney?* Nephrectomy is indicated when the creatinine clearance provided by the affected kidney, if it were isolated, would not eliminate the need for dialysis. Using percent function as a cutoff, like the commonly cited standard of 10%–15%, may have little meaning, especially if the contralateral kidney exhibits impaired function. In addition, kidneys that function marginally in infancy sometimes assume a progressively smaller portion of overall renal function with interval growth of the affected child, even in the absence of obstruction or infection. An intrinsic developmental insult and/or the rules governing renal hypertrophy, where healthy kidneys do not relinquish the additional renal function they are asked to assume, can be implicated when this occurs.

One area of controversy for some ectopic ureters involves the *management of the lower ureteral segment. In cases of Wolffian or GYN-ectopy, where an element of obstruction is the rule, the lower ureter need not be removed.* Once decompressed, ascending infections of these dry, isolated segments are uncommon and the need for secondary ureterectomies after subtotal ureterectomy is rare. The obstructed ureters found with GU-ectopy typically enter the bladder neck or urethra. These can also

FIGURE 40.29 Reflux into the ureterocele and upper-pole system of the left kidney.

remain, although a small number will predispose to recurrent urinary infections that ultimately necessitate their removal. It may be that such systems begin to reflux after the outflow of urine ceases from above (see the "Voiding Cystourethrography" section above).

Refluxing lower ureters have typically been removed in concert with nephrectomy. An extravesical approach through a second lower transverse muscle-splitting (Gibson) incision adds little additional morbidity. However, the necessity for a simultaneous approach for these variants has been questioned. In a study by Plaire et al.,[89] secondary surgery for removal of the distal ureter was required in only 4 of 38 such patients. Subsequent series have drawn similar conclusions. Long ureteric stumps or those in patients with dysfunctional voiding and incomplete bladder emptying appear to pose the most risk.[90] In cases where a ureteral stump is left, be it refluxing or obstructed, it should be taken as distal as possible and ligated with absorbable sutures, and urine should be aspirated from its distal end before closure. Urinary fistulas have occurred when presumably obstructed ureteral stumps have been left open and unappreciated reflux commences.

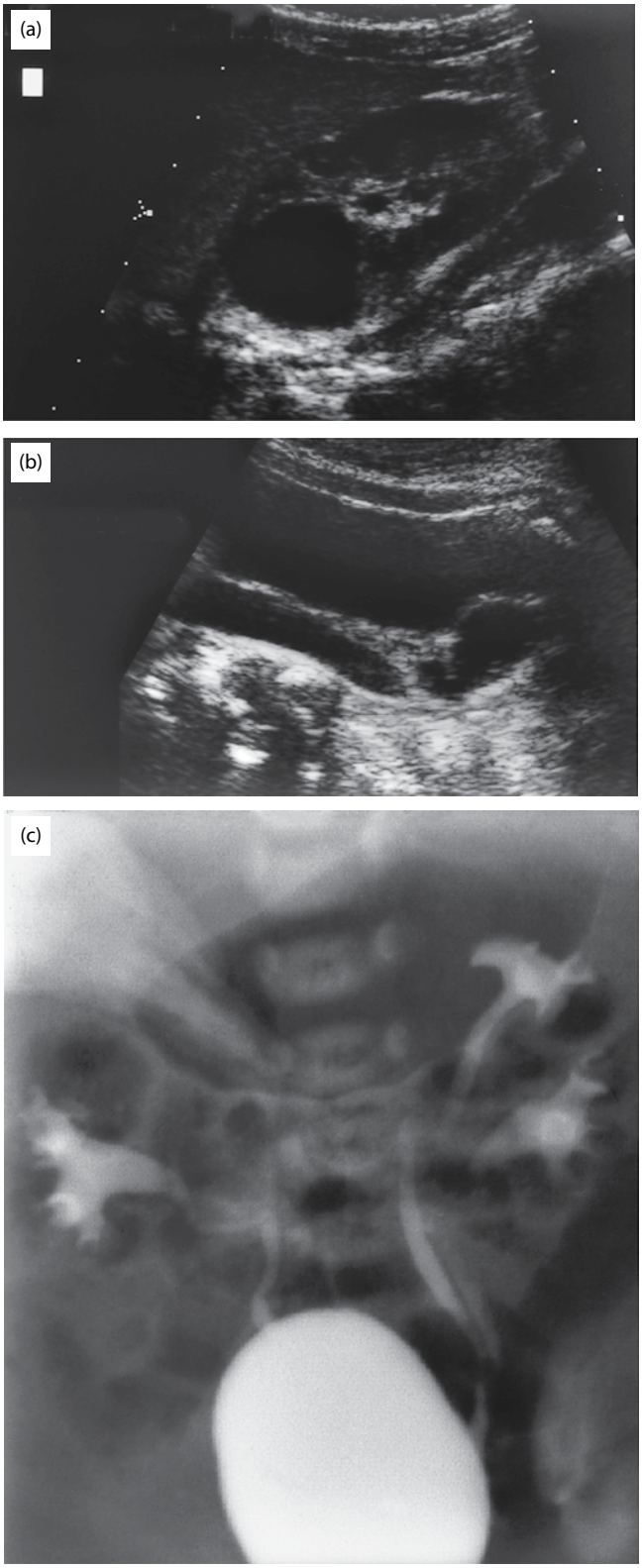


FIGURE 40.30 VUR associated with ectopic ureter to the urethra. (a) Duplex right kidney with hydronephrotic upper pole. (b) An ectopic ureter behind the bladder could be confused with a ureterocele. (c) A voiding cystourethrogram shows reflux into duplicated ureters on the left and the lower pole on the right.

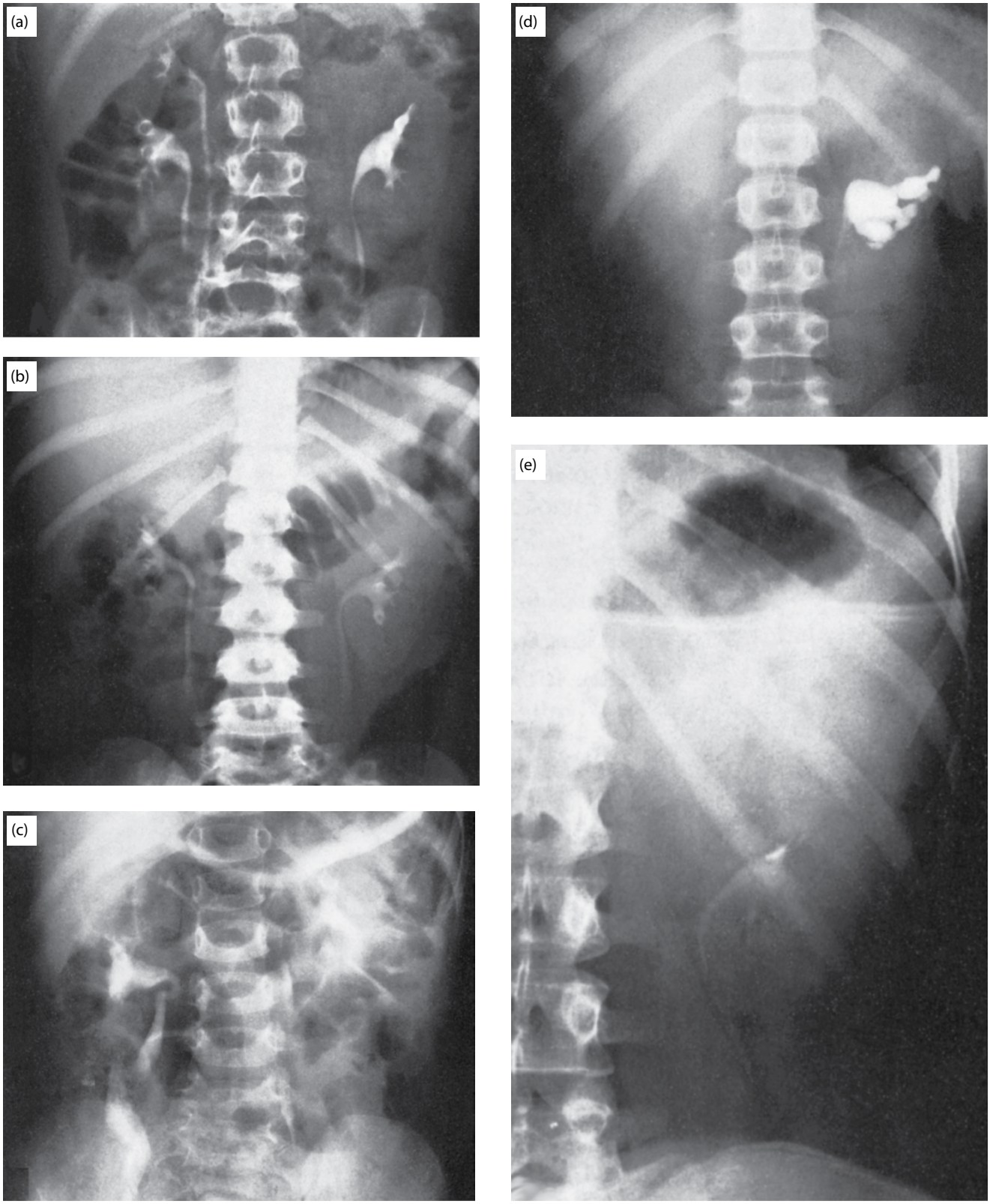


FIGURE 40.31 Examples of characteristic lateral and downward displacement of the lower segment when the functionless upper pole is dilated. (a) Functionless upper left segment. (b) Poorly functioning upper right segment and functionless upper left segment. (c) Functionless upper right segment and displacement of the lower segment. (d) Reflux into the displaced lower-pole segment of the left kidney. (e) Functionless upper left segment simulating tumor in the upper pole.

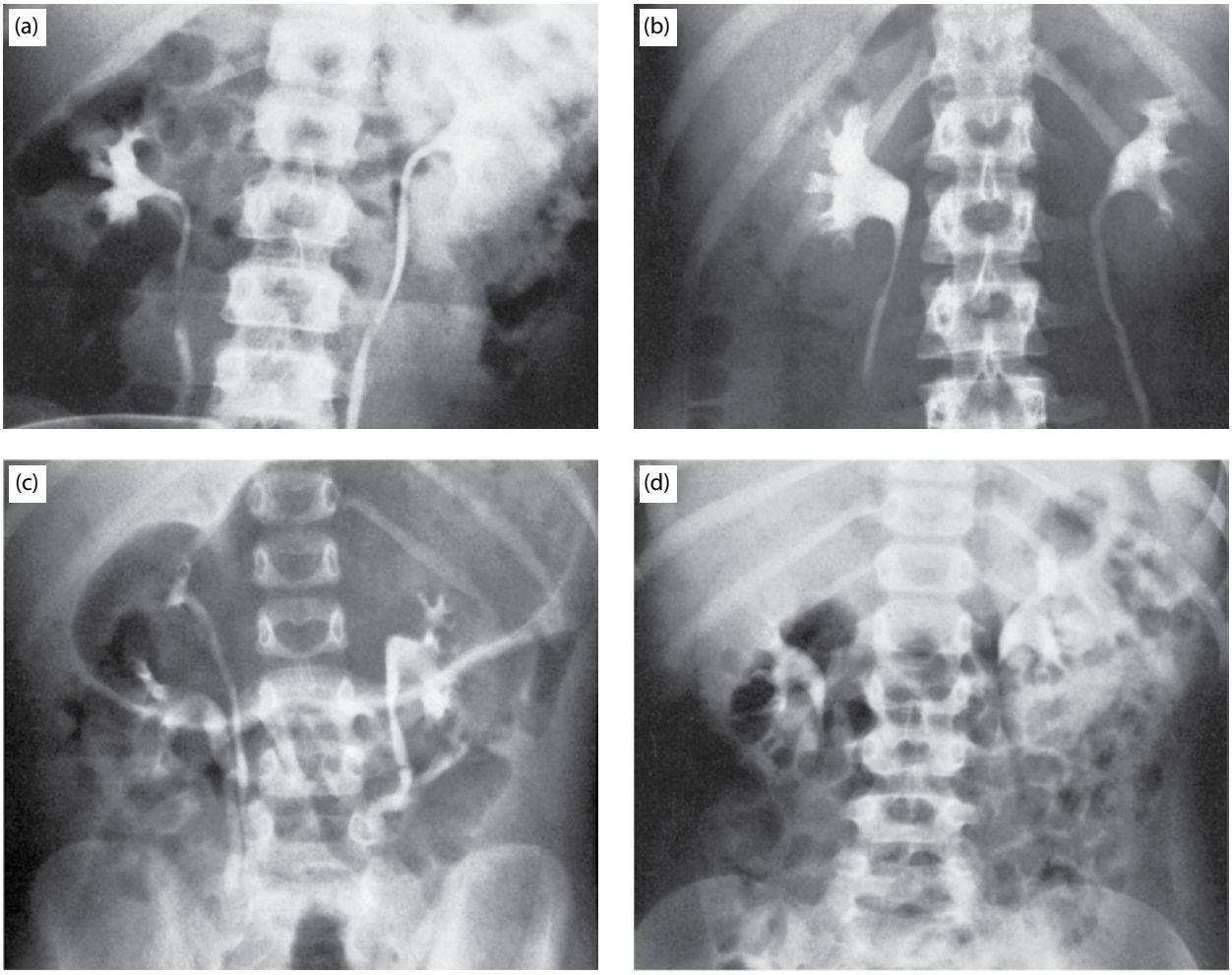


FIGURE 40.32 Appearance of lower-pole pelvis when the upper pole is functionless and nondilated. (a) Functionless upper right segment. The calyceal system of the lower segment is smaller but relatively normal. (b) Functionless upper pole on left with decreased number of calyces of the lower segment. (c) Functionless upper left segment with apparent increase in renal substance of the upper pole. The presence of a duplication of the contralateral kidney is often a key to diagnosis. (d) Functionless upper right segment with apparent increase in renal thickness on the medial side of the upper pole.

Duplex System: Minimal or Nonfunctioning Upper Pole

Partial nephrectomy is recommended for the affected upper pole.[91] The case made for salvage is similar to that in singlets and depends on relative function. Developmentally, the upper "half" of a *normal* duplex kidney typically contributes only one-third of that kidney's glomeruli, or, at most, 16% of overall renal function. The lack of an optimal inductive influence during fetal development, combined with an element of obstruction, significantly reduces the contribution of most upper-pole moieties drained by ectopic ureters. As in single systems, a subtotal ureterectomy is usually sufficient, taking the ectopic ureter as far distal as possible through a flank incision. When there is reflux into the upper pole and concerns about the ureteral stump persist, it can be removed through a second incision. However, as with single systems, most residual ureteral stumps do not present later problems.[92]

Single System: Salvageable Function

Reimplantation of the affected ureter is the treatment of choice. It helps to initially identify the ureter outside the bladder, especially when the insertion of the ectopic meatus cannot be localized cystoscopically. Once the ureter is mobilized, a transvesical or extravesical approach to ureteroneocystostomy can be successfully applied. The distal-most segment that enters the bladder neck or urethra can be disregarded with these and other ectopic ureters. The tedious dissection required of their removal risks damaging the urinary sphincter complex. Ureteral tailoring is often necessary and can be done using any one of a variety of techniques (see Chapter 39 on megaureters).

Duplex System: Salvageable Function

In cases where the upper pole is obstructed, yet provides salvageable function, its ureter can be anastomosed to the adjacent lower-pole renal pelvis (ureteropyelostomy) or ureter (ureteroureterostomy). The lower ureteral segment can be mobilized to the pelvic brim and excised, and the remainder left alone. Concerns about discrepancy in size between the ectopic and recipient ureter are usually unfounded.[93] The long-term efficacy of this approach is

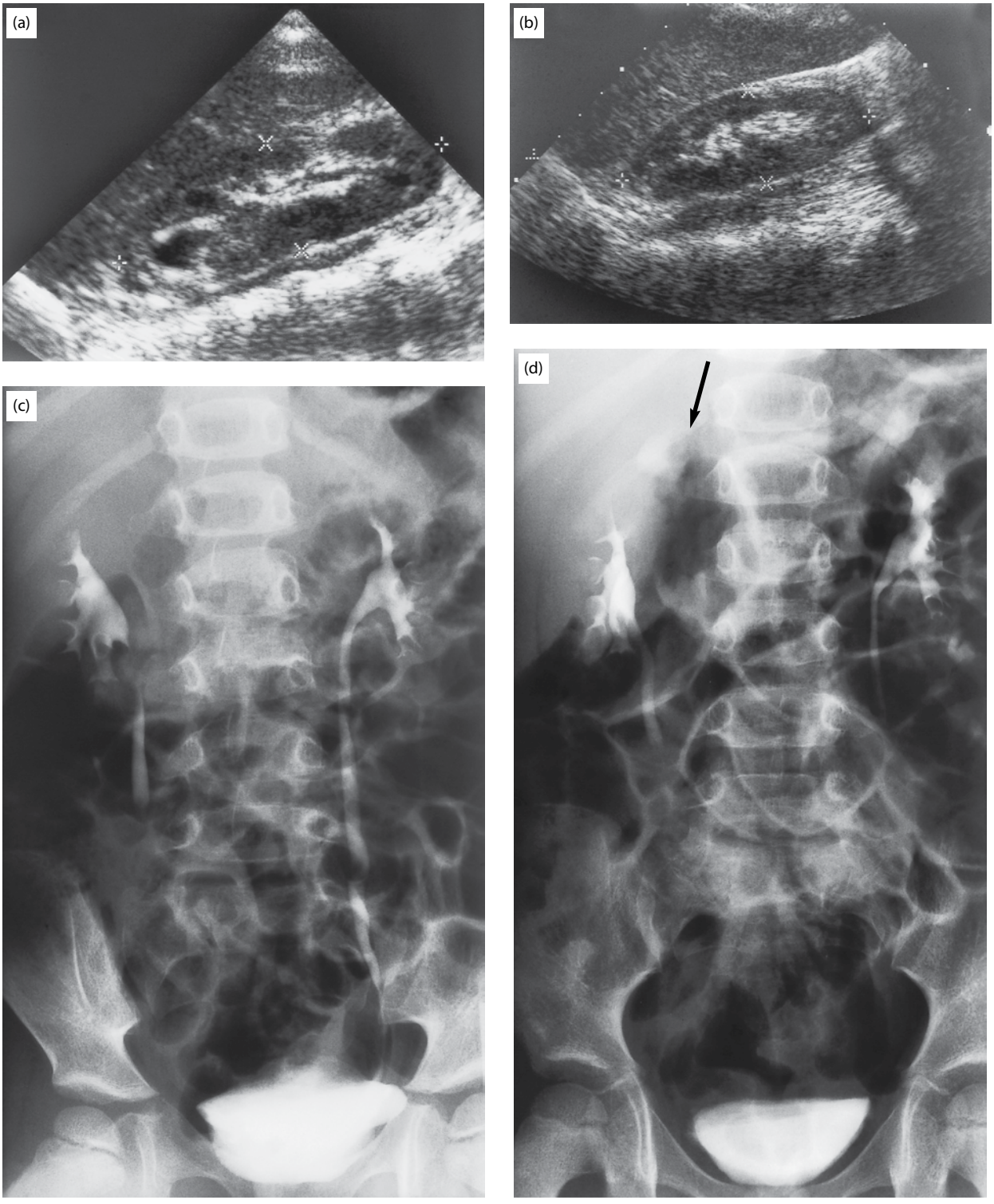


FIGURE 40.33 Utility of EU. Studies in a 13-year-old girl with continuous wetting were strongly suggestive of ectopic ureter. Sonograms for the past 7 years read as normal. (a) Initial ultrasound at 6 years old suggests mild upper-pole dilatation. (b) Current ultrasound is essentially unremarkable. Retrieval and review of early excretory urogram confirms the clinical impression. (c) Note the deviated axis of the right kidney and ureteral displacement on early sequence of the excretory urogram. (d) A later film shows delayed uptake of contrast in the upper pole.

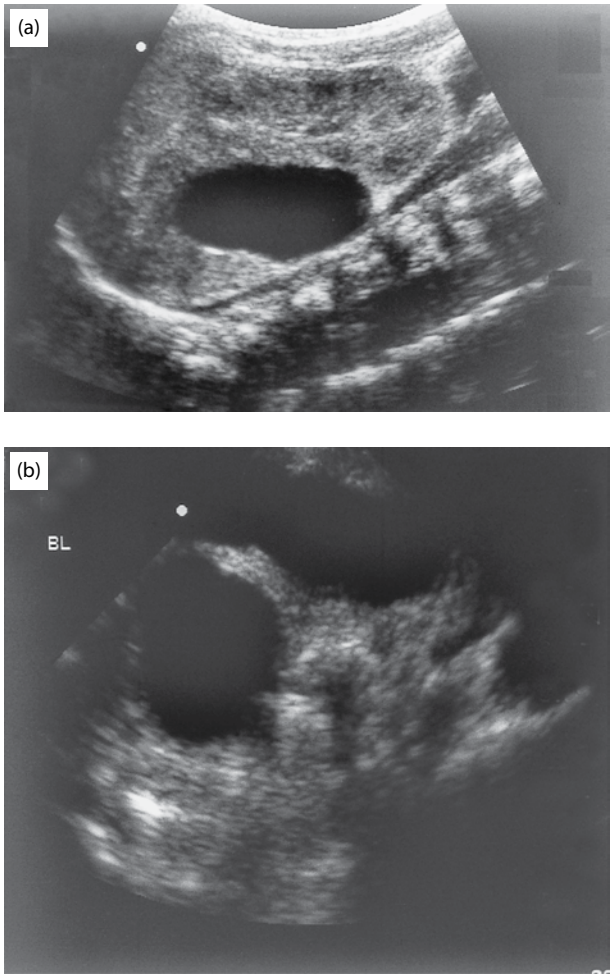


FIGURE 40.34 Infant boy with UTI. The role of EU. (a) Ultrasonogram initially felt to represent single-system hydronephrotic right kidney. (b) A pelvic sonogram demonstrates a markedly dilated ureter behind the bladder. (c) EU shows the displaced lower pole of the right kidney.

TABLE 40.4 Excretory urography

Findings suggesting occult duplex kidney with ectopic ureter

1. *"Drooping lily sign"*—Inferior and lateral displacement of lower pole by minimally/nonfunctioning upper pole. Delayed films may show function, although most are "silent." Axes of the kidneys should normally cross the body of the 10th thoracic vertebrae.
2. *Lateral displacement of lower-pole ureter*—Compared with contralateral ureter, differences in the distance from an adjacent vertebral pedicle.
3. "Missing calyx"—Incomplete complement of calyces with absence of system draining upper pole. A shortened or cutoff infundibulum to the upper-pole calyx, which is normally the longest.
4. More upper-pole parenchyma than expected with increased renal length.
5. Duplex kidney on the contralateral side.
6. Dilated, ectopic ureter appreciated on postvoid film.

documented.[94] These operations are usually no more challenging than the dismembered pyeloplasties required of infants with ureteropelvic junction obstructions. Rates of success should be similar. When technical concerns persist or if the upper-pole moiety exhibits signs of cystic dysplasia, a partial nephrectomy is recommended. Visualization of the upper-pole moiety in assessment of dysplasia is one advantage of this approach. Renal-sparing surgeries could probably be utilized more frequently in this setting. In one study, normal histology was found in 57% of upper-pole partial nephrectomy specimens removed from ectopic ureters.[91]

Another option for obstructed systems is to approach the duplication from below. *When reflux is present in one or both ureters*, a common sheath ureteral reimplantation is the preferred method of treatment.[95] The repair can be technically challenging, especially in smaller infants. Tailoring of the upper-pole ureter

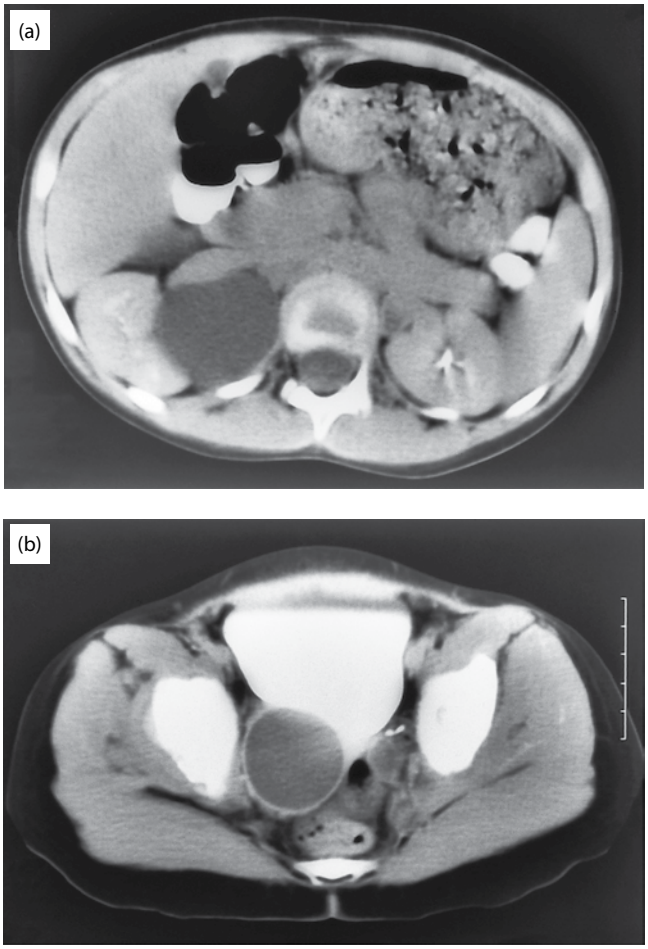


FIGURE 40.35 CT in a female toddler with abdominal pain and palpable mass. (a) Markedly dilated ureter displacing the right kidney associated with duplication. (b) The ureter is shown behind the bladder.

usually becomes necessary to achieve the desired length–diameter ratio required of successful ureteroneocystostomy. Revisions are made along the length of the ureter opposite the common wall, where vascularity is shared by the duplication. Where folding techniques result in excessive bulk with larger ureters, excisional tapering is preferred.[96] A psoas hitch is sometimes necessary to gain additional length for the reimplantation. Another option for duplications with an obstructed upper-pole ureter and refluxing lower-pole ureter is to perform a proximal diversion of the upper ureter (ureteropyleostomy), discard its remainder, and reimplant the lower-pole ureter alone. Although two incisions are required of this approach, it avoids the technical challenge that accompanies ureteroneocystotomy of duplex ureters, where one or both may be dilated.

Recommendations for Management: Ureteroceles

Single System: Minimal or Nonfunctioning Kidney

Nephrectomy is the treatment of choice. Ordinarily, the ureterocele remains collapsed after aspiration and any element of obstruction to the bladder neck or contralateral ureter resolves (Figure 40.37). The latter may unmask reflux into the contralateral, now solitary, kidney. With larger ureteroceles, a significant reservoir for lower UTIs remains, despite their decompression. Although not well defined in the literature, some of these eventually require secondary surgery for their removal. Cystoscopic evidence of the open orifice typically accompanying sphincteric or cecoureteroceles will identify those variants particularly at risk for future problems, especially in females. When this is the case, simultaneous excision of the ureterocele with bladder reconstruction is reasonable, if the age of the patient permits. Otherwise, the patient can be followed medically after nephrectomy and repair of the bladder deferred to a later age, if indicated.

Whether antenatal diagnosis alters the long-term implications of such anomalies is unclear. A nonoperative approach has been taken in a small group of infants whose ureteroceles subtended multicystic dysplastic kidneys. In limited follow-up, the ureterocele collapsed or remained stable in each case, whereas ipsilateral kidneys uniformly involuted. None required surgery.[18]

Selective cystoscopic puncture should probably not be considered for obstructed ureteroceles associated with a nonfunctioning kidney. This risks converting the anomaly from one that can be potentially addressed solely from above to one requiring another incision to correct a refluxing ureterocele. Nonselective cystoscopic "unroofing," as advocated by Tank,[97] remains an option for decompressing obstructed ureteroceles in children who are extremely ill and unable to tolerate open surgery. Interestingly, 50% of renal moieties that showed no function on EU subsequently demonstrated excretion of contrast after their decompression. These data suggest that some kidneys may recover function after being vented, but more likely point to the shortcomings of EU compared with radionuclide studies in infants with obstructed kidneys. Reflux is an expected sequela of this predecessor of selective puncture.[98] Decompression can also be achieved with percutaneous drainage, which can serve to temporize until the ureterocele can be definitively addressed.[99]

Single System: Functioning Kidney

The experience with *selective incisions or puncture* of these ureterocele variants has been encouraging enough that it should be considered the procedure of choice, when obstruction warrants (Figure 40.38).[72,100] In one series, for example, endoscopic decompression was successful in 22 of 25 patients (88%) with single-system intravesical ureteroceles.[101] Reflux tends to appear in larger ureteroceles whose associated detrusor defects result in very little backing to the anomaly. Ureterocele excision, ureteral reimplantation, and correction of any detrusor defects may become necessary when reflux appears, although a trial of medical management, similar to that used with primary VUR, is reasonable, especially in younger children, providing infection can be avoided.

Duplex System: Minimal or Nonfunctioning Upper Pole

An upper-pole partial nephrectomy is a very reasonable option but might not finalize the problem (Figures 40.39

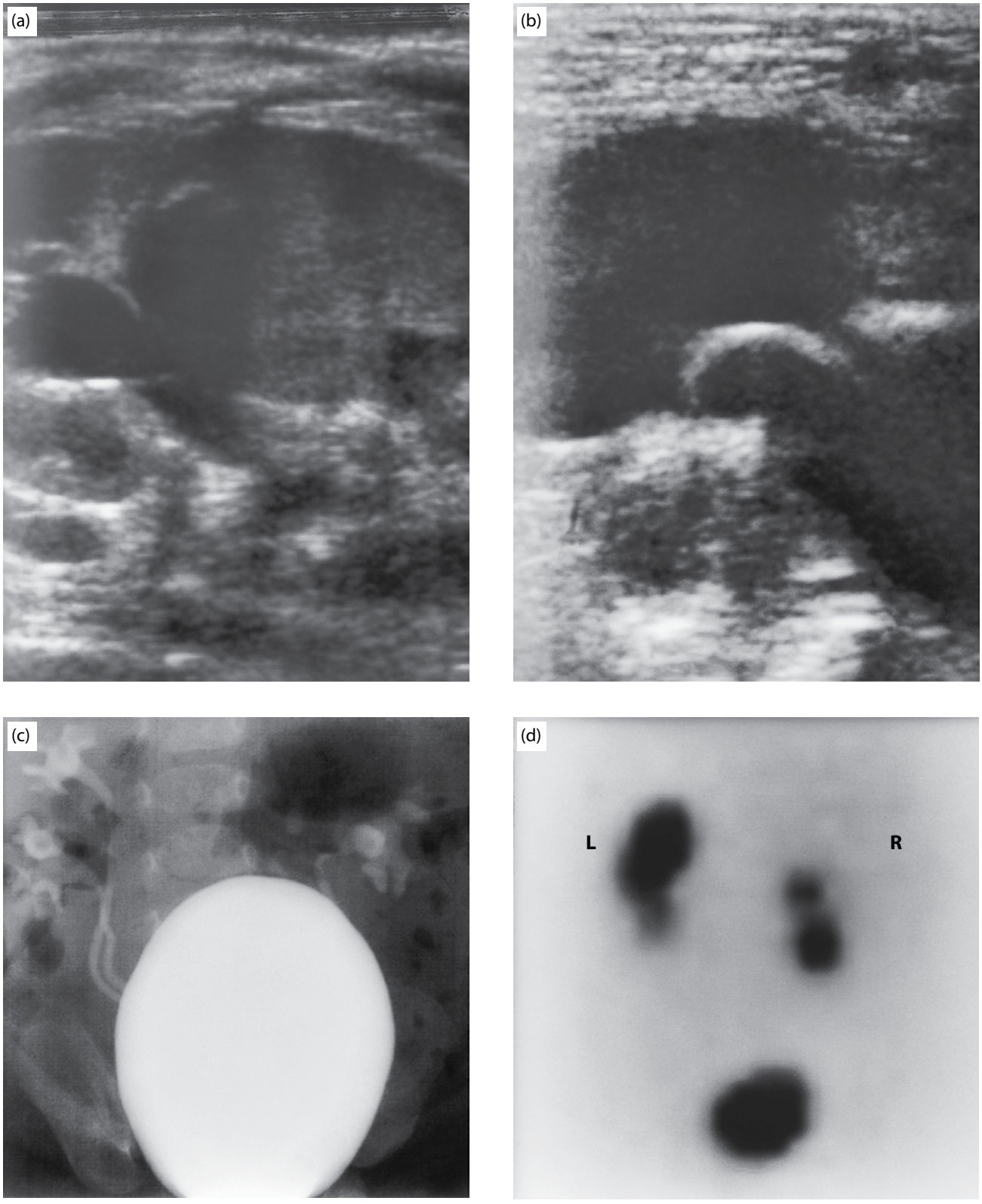


FIGURE 40.36 Antenatally diagnosed ureterocele in a newborn girl. (a) The sonogram shows a dilated upper-pole segment of the duplex left kidney. (b) Pelvic view of the ureterocele projecting within the bladder. (c) A cystogram demonstrates reflux into the contralateral duplex ureters and lower-pole ureter on the left. (d) A renal scan shows preservation of function and hydronephrosis of the left upper-pole moiety.

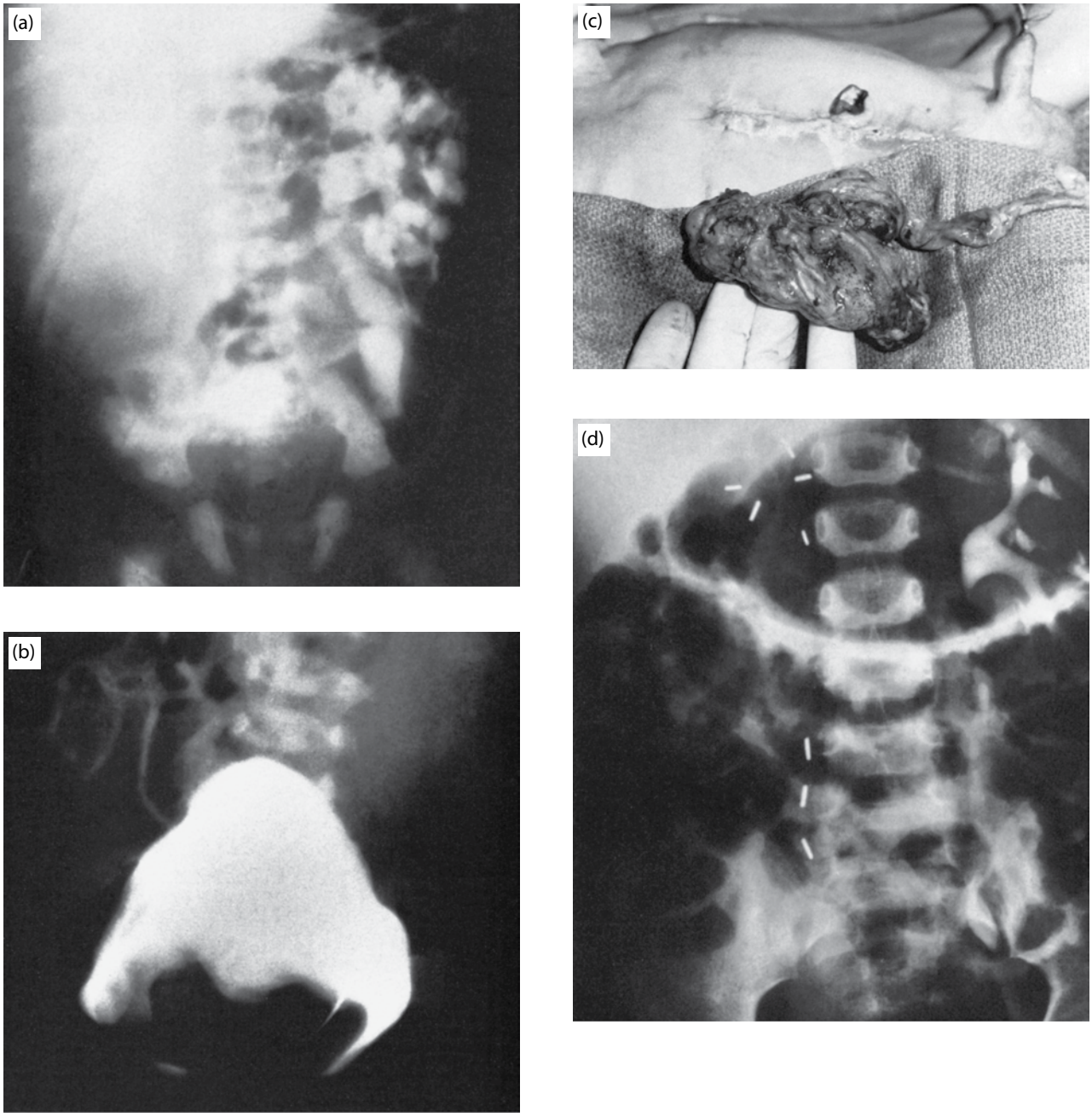


FIGURE 40.37 Newborn male with large single-system ureterocele of the right side. (a) An excretory urogram shows poor visualization of the right collecting system and hydronephrosis of the left. (b) A cystogram shows a large ureterocele filling the bladder and extending through the bladder neck. (c) At surgery, the grossly dyplastic hydronephrotic kidney was removed and extravesical dissection of the ureterocele was completed. (d) A postoperative excretory urogram shows significant improvement of the left-sided hydronephrosis and collapse of the ureterocele.

and 40.40). This *upper tract approach* usually effectively decompresses the ureterocele, potentially restores trigonal anatomy, and may be the only treatment needed for some patients.[102,103] In the series reported by Caldamone et al.,[15] 7 of 36 patients (19%) ultimately required secondary procedures for persistent reflux (3 patients) or bladder outlet obstruction (4 patients). VUR appeared in 10 cases after decompression, where none was present beforehand. The reflux resolved in three patients. Long-term outcomes into adulthood are unavailable in the literature. Other clinicians report similar rates (about 20%) of persistent reflux into ipsilateral lower-pole or contralateral ureters after partial nephrectomy alone.[42,104] In another series of 19 patients reported by Scherz et al.,[105] 9 patients (47%) required secondary intravesical surgery for UTI or VUR (Figure 40.41).

These types of outcomes led some clinicians to advocate a *combined "up-and-down" approach* where heminephrectomy, ureterocele excision, and ureteral reimplantation are completed in a single surgery.[44,106] The need

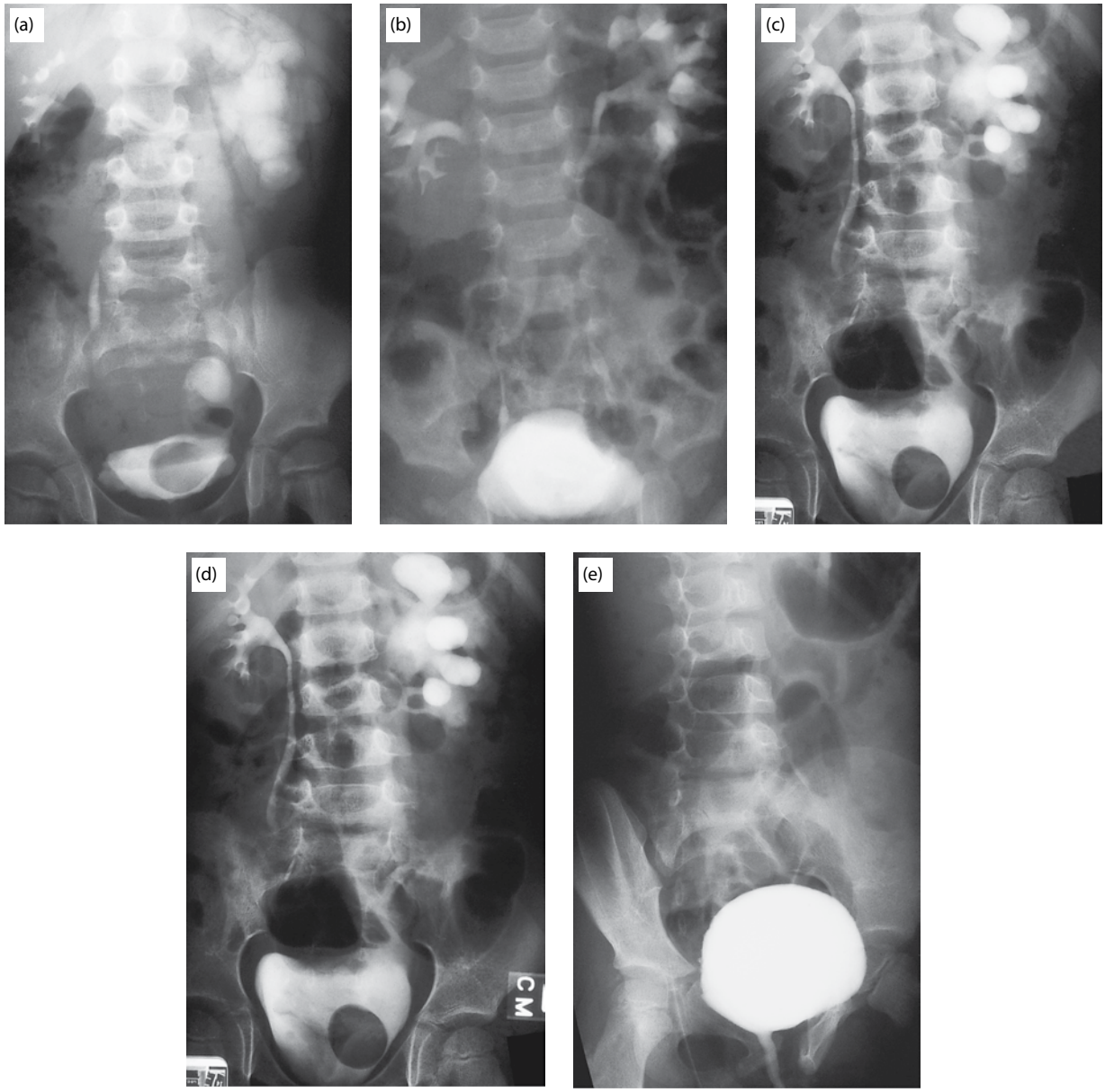


FIGURE 40.38 (a) Single-system intravesical ureterocele causing significant hydroureteronephrosis of the left collecting system. (b) After incision, marked improvement in the degree of dilatation is seen. No reflux was present before or after surgery. (c) A similar variant with hydronephrosis of the left kidney treated with selective incision. (d) Significant improvement shown after surgery. (e) The voiding cystourethrogram is unremarkable.

for secondary surgeries is far less common with the combined approach. For example, only 14% of patients in the Scherz series[105] required reoperations for persistent reflux after the combined approach. To its detriment, ureterocele excision and duplex ureteral reimplantation can present a technical tour-de-force in infants and small children. In addition, intravesical repairs are unnecessary in perhaps half of these patients. The characteristics of ureteroceles that ultimately require excision and bladder reconstruction remain to be fully defined. Such selection criteria would help identify patients whose problem would be best finalized by the upper tract approach and limit the combined approach for those that truly need it.

The review by Husmann et al.,[107] which assessed response to treatment based on renal unit jeopardy, offered insight in this regard. Of 87 patients with a ureterocele and nonfunctioning upper pole treated by heminephrectomy, subtotal ureterectomy, and observation (initial upper tract–alone approach), 54 (62%) required additional surgery to correct reflux. Notably, the need for additional surgery was directly related to the number of renal moieties that had VUR present. When ureterocele alone was present, 21 of 21 patients required no further surgery. If low-grade reflux (less than III/V) was present in only one ureter, 8 of 15 patients (53%) did well with the upper tract–alone approach. Finally, and most significantly,

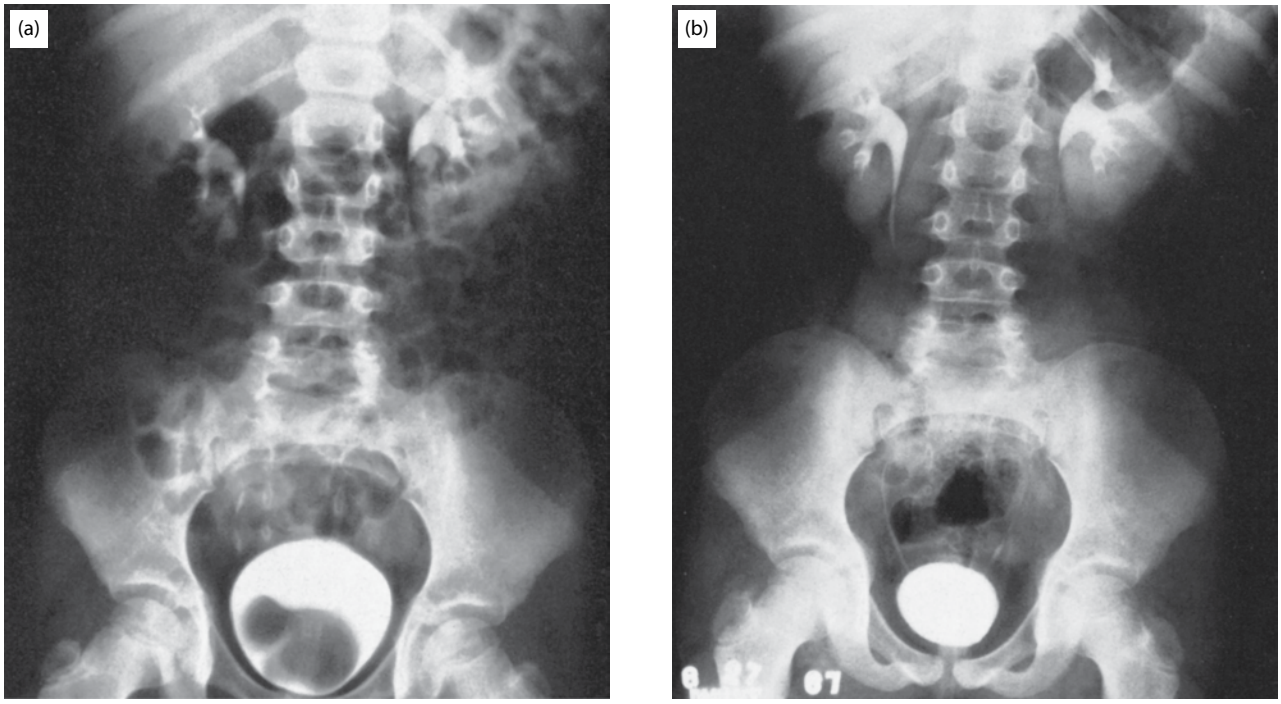


FIGURE 40.39 (a) A preoperative view shows minimally functioning upper-pole moiety of the right kidney. (b) A postoperative view shows decompression of the ureterocele and an essentially normal right kidney.

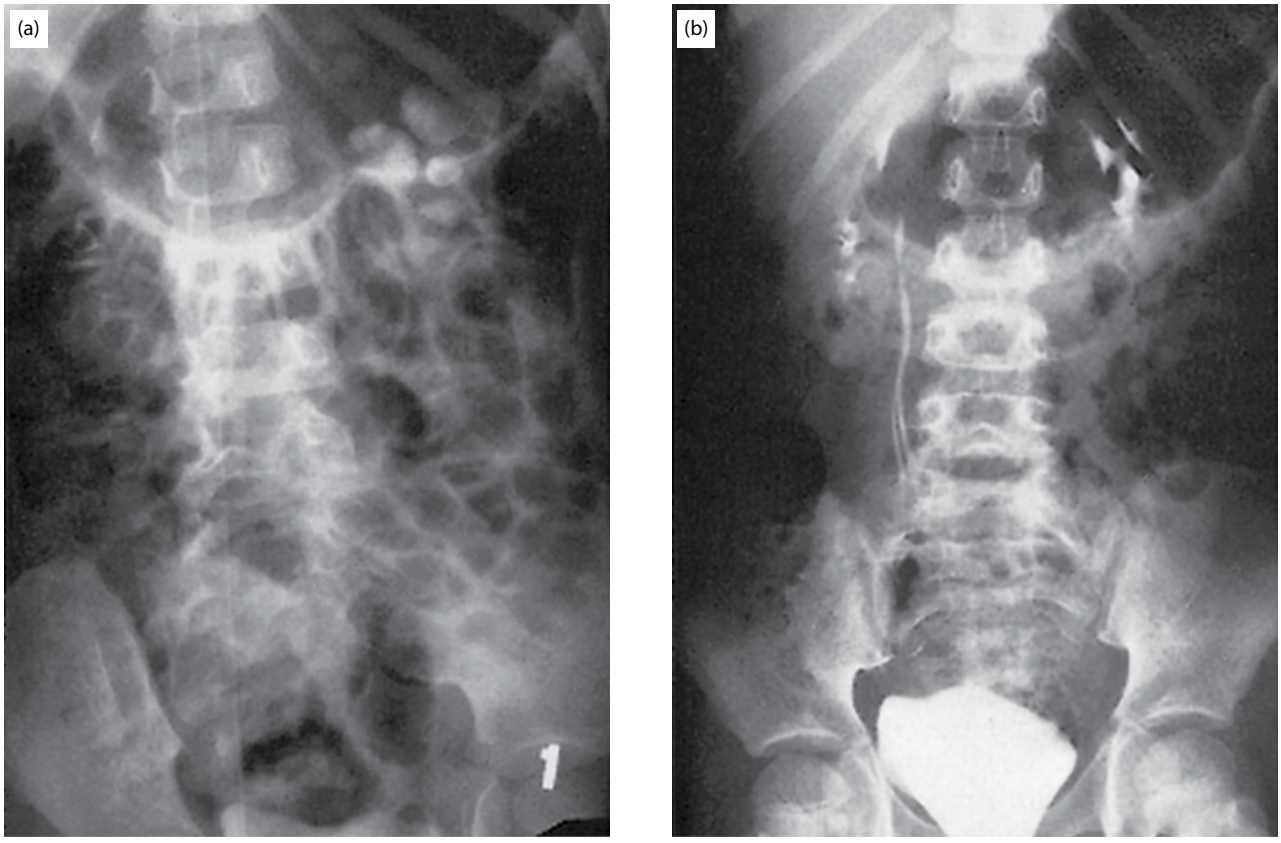


FIGURE 40.40 Extravesical ureterocele treated by heminephrectomy and subtotal ureterectomy. (a) A preoperative excretory urogram shows a left-sided anomaly and markedly hydronephrotic lower pole. (b) Postoperative view. Preservation of the function and appearance of the remaining kidney is often surprisingly good. The ureterocele is fully decompressed.

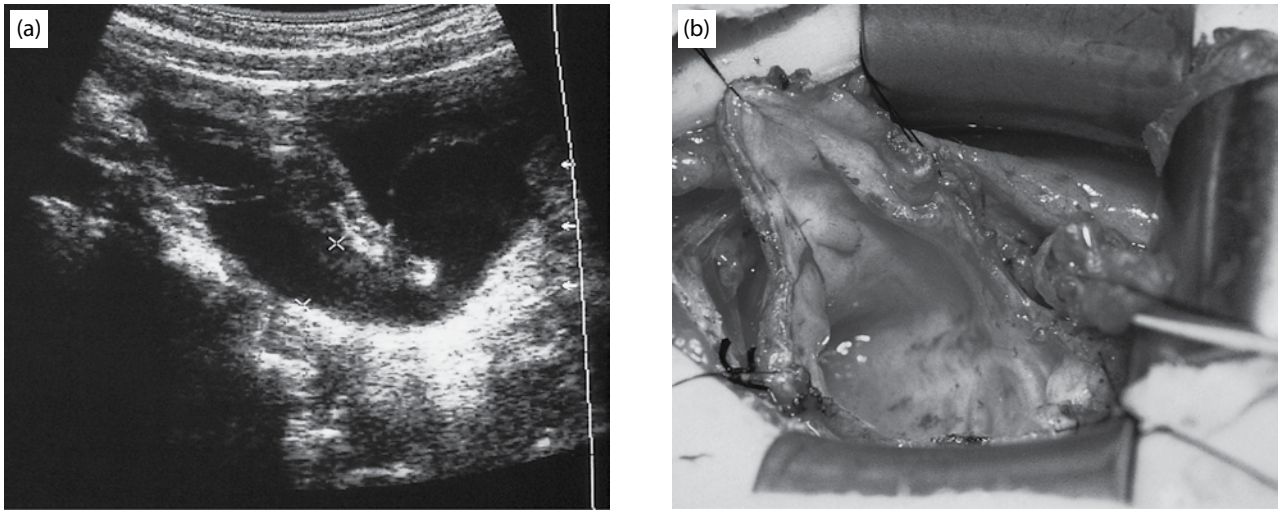


FIGURE 40.41 (a) The stump of the residual ureter and ureterocele remain after heminephrectomy. The patient presented with recurrent urinary infections. (b) Large ureterocele opened at surgery.

when high-grade reflux was seen in one ureter or reflux was associated with more than one moiety, regardless of grade, surgery became inevitable for 48 of 50 (96%) patients. A subsequent review by DeFoor et al.[108] echoed similar findings. Simply put, ureteroceles whose bladder involvement affects other renal segments are more likely to require secondary surgery. Ureterocele prolapse is another finding that inevitably portends bladder reconstruction.[109] In addition, the occasional ureterocele that itself refluxes at presentation will, by default, require a combined up-and-down approach for management.

Given these data, families and patients can be better informed as to the likelihood of needing lower urinary tract surgery if an upper tract approach is initially used. In addition, strong consideration is given to a complete urinary tract reconstruction if the preoperative workup returns such ominous prognosticators and the patient's size permits. Finally, nonselectively unroofing the ureterocele becomes a very real option in newborns and small infants who are destined to require up-and-down surgery anyways, if the "clinical staging" of their anomaly is strongly suggestive. Eliminating obstruction significantly lessens the threat of urinary infections, and decompression of the ureterocele simplifies the bladder repair (Figure 40.42).[166]

Most children can be effectively managed with antibiotic prophylaxis until they are old enough to have definitive reconstructive surgery. However, infections can still occur. In one series of 15 neonates with ureteroceles, 8 developed infections during the first few days of life, including 3 who were receiving prophylactic antibiotics.[110] Assessment, with considerations to surgery, should be done at an early age to optimize the care given to children whose anomalies have been discovered antenatally.[111] The advantage of prenatal detection is demonstrated by one retrospective study comparing the occurrence of UTIs in 95 children with ureteroceles in duplex systems. UTIs occurred much less frequently with antenatal detection (12% vs. 84%) both before and after (15% vs. 27%) surgery.[112] Secondary procedures were also less common (20% vs. 46%).

The report by Gran et al.[113] offers a unique alternative in management. The *lower tract–alone approach* eliminates the long-term follow-up required of residual ureteroceles that remain after the upper tract–alone approach. Rather than remove the nonfunctioning renal moiety, sole reconstruction of the involved ureters and the bladder was successfully completed in 16 patients. No morbidity (mean 5 years' follow-up) has been associated with the nonfunctioning portions of the kidney that remain. Detractors, concerned with the preservation of possibly dysplastic tissue, will argue that families are now offered extended follow-up of such kidneys in exchange for that of the bladder. However, if parallels are drawn with the relative benefits of removing asymptomatic multicystic dysplastic kidneys, the argument may ultimately prove to be a weak one. Future management may see many children with ureteroceles initially punctured and decompressed during the newborn period until they are old enough for bladder reconstruction, if reflux persists or appears, regardless of the status of their kidneys.

Finally, and to further cloud the recommendations in management, an expectant "observation-alone" approach has been used with success in some children with a nonfunctioning upper-pole moiety and low-grade lower-pole VUR. In a group of 52 such patients, whose anomalies were detected antenatally, 14 (27%) were managed expectantly and did well, with a median of 8 years of follow-up.[114] Each was kept on prophylactic antibiotics until the completion of toilet training, and none required surgery through a median follow-up of 8 years. Watchful waiting has also been used in children whose ureteroceles subtend functioning renal units. In most cases, dilatation and reflux both improved with time.[115] This appears to be especially true of ureteroceles that are not significantly obstructed, as shown by scintigraphy.[116] Patients whose ureteroceles subtend dysplastic moieties in duplications have also been followed conservatively.[18] The long-term

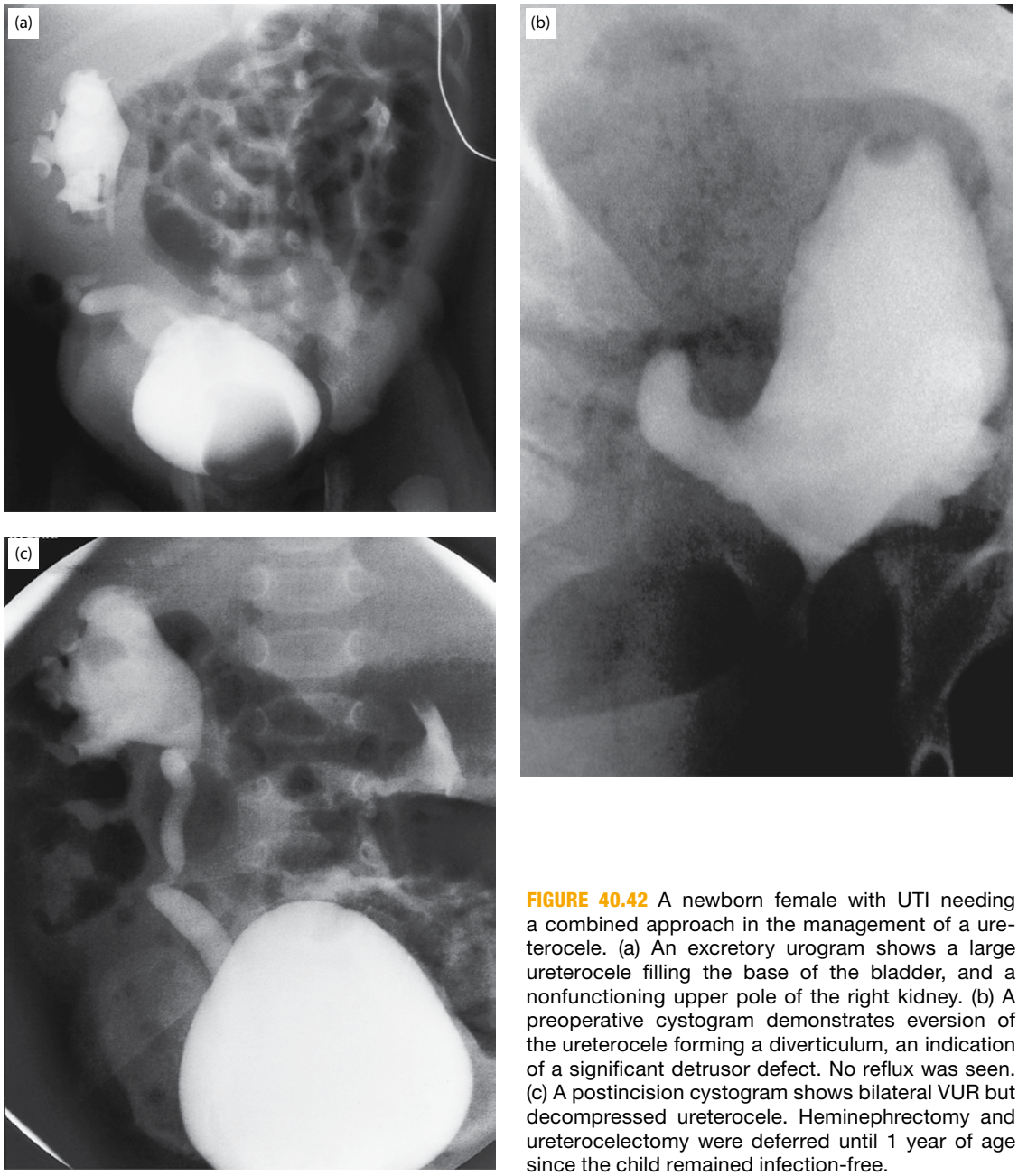


FIGURE 40.42 A newborn female with UTI needing a combined approach in the management of a ureterocele. (a) An excretory urogram shows a large ureterocele filling the base of the bladder, and a nonfunctioning upper pole of the right kidney. (b) A preoperative cystogram demonstrates eversion of the ureterocele forming a diverticulum, an indication of a significant detrusor defect. No reflux was seen. (c) A postincision cystogram shows bilateral VUR but decompressed ureterocele. Heminephrectomy and ureterocelectomy were deferred until 1 year of age since the child remained infection-free.

implications of these findings raise more questions than they answer. Affected children would appear to continue to be at risk for the morbidity seen before the advent of antenatal detection. However, prenatal detection appears to be rewriting the natural history of some ureteroceles, as it has with other congenital urinary anomalies.

Duplex System: Functioning Upper Pole

Like their nonfunctioning partners, these conditions too can be addressed with an upper tract–alone approach. It should be remembered that upper-pole duplications optimally contribute perhaps 16% of overall renal function. Because of this somewhat marginal contribution, some clinicians recommend partial nephrectomies for the majority of functioning duplications, whether they function or not. This avoids the potential complications of the reconstruction, risks to the lower pole, and the unknown long-term implications of upper-pole parenchymal salvage.[31] The other option is salvage of the upper pole by creating a diverting ureteropyelostomy or ureteroureterostomy in combination with a subtotal ureterectomy. A study similar to that cited above for nonfunctioning duplications treated with an upper tract approach has not been reported. Nevertheless, there is every reason to believe that the same risk factors for persistent reflux and recurrent urinary infections exist and result from the size and position of the ureterocele and its implications for the trigone and adjacent ureters. With this in mind, the upper tract approach is usually reserved for ureteroceles

presenting without reflux into the ipsilateral lower and contralateral ureters and should offer a high likelihood of success.

In patients whose variants have associated VUR, it seems reasonable to address the majority solely at the bladder level, removing the ureterocele and correcting the reflux, thus eliminating the need for secondary surgery. Such an approach is ideal for the older child whose bladder is large enough to allow a complex reconstruction with a high likelihood of success. The reality is, however, that the majority of ureteroceles are diagnosed antenatally. After birth, such babies remain at significant risk, as UTIs associated with obstruction are much more threatening to the child and kidney than those that occur with reflux alone. In addition, the affected kidney potentially incurs progressive damage because of distal ureteral obstruction. As a result, medical management with prophylactic antibiotics should be considered a short-term approach in management rather than an extended panacea. Such an approach may not allow a sufficient enough interval of time until the bladder can be safely reconstructed.

As an alternative, endoscopic treatment provides an effective option for many newborns and infants, particularly those who present with significant UTIs. Surgeons should hold realistic expectations for this approach, however, since it rarely provides the final solution for these types of ureteroceles, even with selective incision. The success of endoscopic decompression and the need for reoperation appear to be dependent on the location of the ureterocele.[117] Selective endoscopic decompression is definitive for 80%–90% of intravesical ureteroceles. In contrast, only 25%–30% of extravesical variants are effectively treated. For most patients with the latter then, the maneuver should be considered a temporizing measure used to vent the obstructed system. This increases the likelihood of success with medical management, thus allowing for additional growth of the child until a definitive bladder reconstruction can be completed (Figure 40.43). VUR persists or appears after decompression in the majority of cases. For example, in one series 18 of 21 (86%) patients with extravesical ureteroceles treated endoscopically required additional surgery. By contrast, the results with intravesical variants were strikingly different, with 14 of 16 children successfully treated with incision alone.[118] In a larger series reported by Husmann et al.,[101] the performance of selective incision was also discouraging. Ectopic ureteroceles preoperatively associated with reflux into one or more moieties required further surgery for persistent reflux in 37 of 44 (84%) cases. An identical reoperation rate occurred when partial nephrectomy was used for

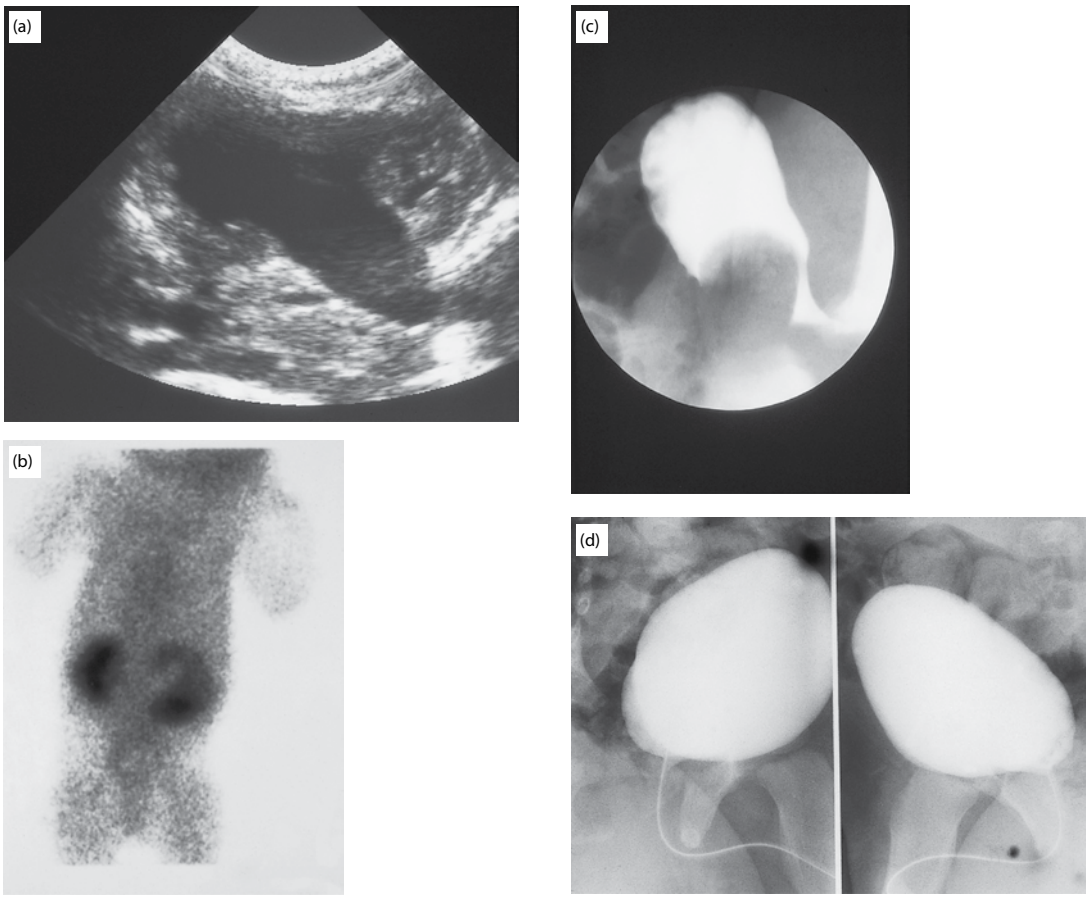


FIGURE 40.43 Selective incision of duplex-system ureterocele with salvagable upper-pole function. (a) Ultrasonic appearance in a newborn diagnosed antenatally. (b) A radionuclide scan shows function to the upper pole and filling defect within the bladder. (c) The bladder defect shown in the cystogram appears largely intravesical, which may have been a factor in success. (d) A postincision cystogram shows no evidence of reflux. Hydronephrosis had virtually resolved.

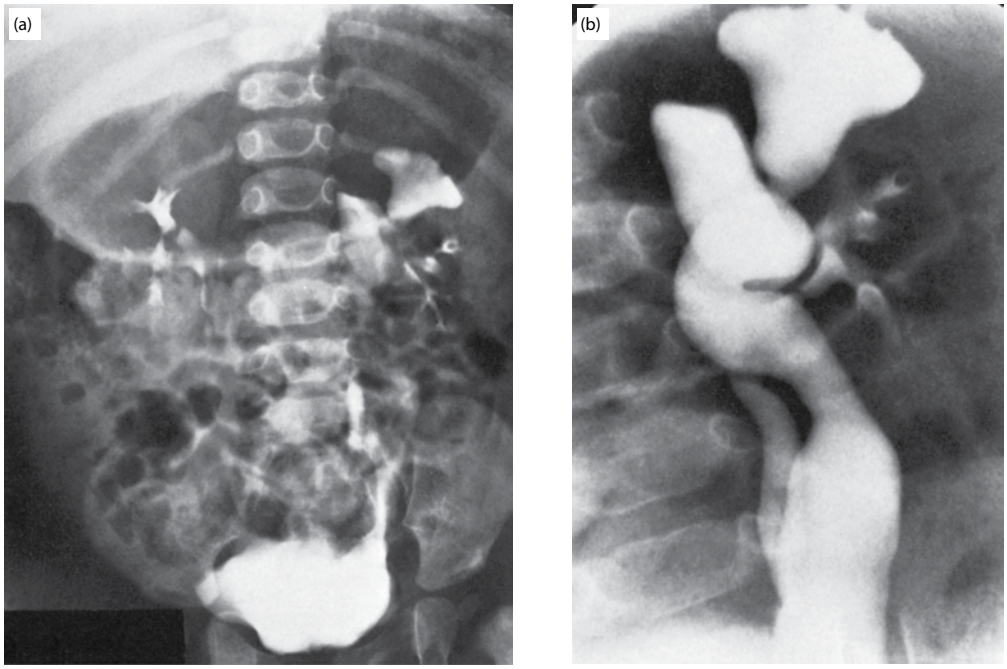


FIGURE 40.44 Risk of ureterocele incision. (a) Duplication of the left kidney associated with an extravesical ureterocele seen on EU. (b) After incision, the previously "obstructed" system converted to one that significantly refluxes into both ureters.

similar variants. In contrast, however, when VUR was not present prior to treatment, incision was more likely than partial nephrectomy to result in the appearance of reflux (64% vs. 15%). Based on this observation, it may be that diverting the ureterocele with a ureteropyelostomy or ureterostomy is the treatment of choice when a salvageable duplex system is not accompanied by reflux.

Whereas success rates with endoscopic incision vary, its weaker performance with extravesical and ectopic ureteroceles is repeatedly borne out in the literature[72,100,119,120] and is more likely a reflection of the anatomic and functional characteristics of the ureterocele and bladder rather than the technique used (Figures 40.44 and 40.45). An unpredictably variable response was offered by the retrospective series reported by Jesus et al.[121] of 50 patients with duplex-system ureteroceles. New-onset VUR occurred postoperatively in 24 patients (40%), mainly to the ipsilateral lower pole or contralateral kidney, findings felt to be unrelated to the puncture itself. Resolution or improvement of reflux occurred in 16 of 22 patients (72%) having prepuncture VUR.[121] Close surveillance is warranted after puncture, and a number of cases of postpuncture VUR will improve.

When VUR persists, the endoscopic injection of bulking agents has been shown to be effective in some cases.[122] Ureterocele puncture was completed in a large series of 109 children, 97 (89%) of which were part of a duplex system. VUR was seen in 85 units before puncture (lower-pole ipsilateral in 53, contralateral in 32). Reflux resolved in 36 (42%) of these. When significant VUR persisted, endoscopic injection therapy was successful for 31 of 44 (70%) units after a single injection and resolved after a second injection in 9 (21%) others. The long-term efficacy of an all-endoscopic approach is unclear, but the attractiveness of its minimally invasive nature is readily obvious.[123]

SURGICAL TECHNIQUES

Although many of these techniques are described elsewhere, observations of their application to the treatment of ectopic ureters and ureteroceles in children deserve comment.

Ureterocele Prolapse

The prolapsed ureterocele is not the surgical emergency once supposed. Manual reduction back into the bladder is sometimes possible, but because of the nature of the defect, it is likely to recur. Heminephrectomy to decompress the ureterocele is another option. However, because of the size of these defects, affected bladders will uniformly require secondary reconstructions as well. A simpler solution is to incise the ureterocele at the bedside with a disposable ophthalmic cautery unit. This technique is usually effective and serves the same purpose as cystoscopic incision. In occasional cases, the latter still becomes necessary to treat the intravesical portions of a prolapsing ureterocele that sometimes fail to decompress because of bladder neck obstruction.

Selective Cystoscopic Incision

The cystoscope is initially passed under vision to avoid traumatizing the ureterocele. For *intravesical variants*, a distally positioned puncture at the ureterocele's medial base is usually sufficient to decompress the structure yet preserve enough submucosal length to maintain the characteristics required of an effective flap valve to avoid reflux (Figures 40.46 and 40.47).[124] *Cecoureteroceles and sphincteric ureteroceles* can be unobstructed by vertically incising

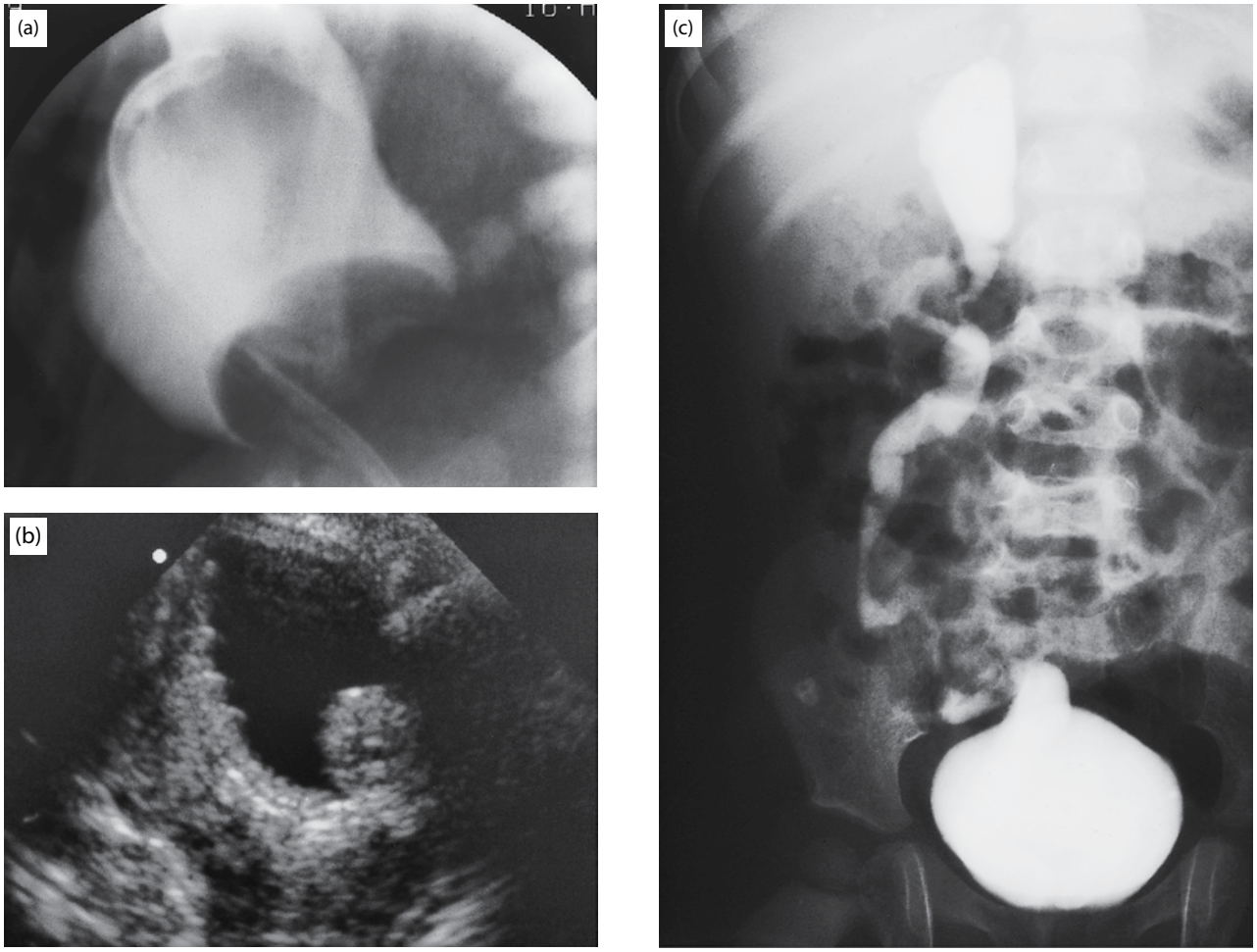


FIGURE 40.45 (a) Large extravesical ureterocele shown during cystography. Both poles functioned and no reflux was seen. (b) Successful decompression is seen by ultrasound, but (c) reflux into upper-pole moiety is documented on a postoperative cytogram.

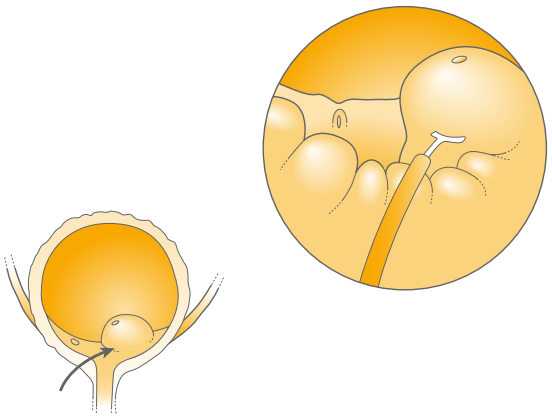


FIGURE 40.46 Endoscopic incision of ureterocele with fine bugbee or wire at the medial base of the ureterocele. (Adapted from Rich MA et al. *J Urol* 1990;144:120.)

the meatus and extending its opening above the bladder neck (Figure 40.48). Cutting current is applied across a No. 3 Fr bugbee electrode to provide a clean, full-thickness puncture of the ureterocele wall. A laser incision can also be considered.[125] Aggressive hydration and minimal instillation of irrigation help keep the ureterocele distended to aid in placement of the puncture. Surgery can be done as an outpatient, depending on age. An ultrasound obtained 10–14 days later should document resolution of hydronephrosis and ureterocele decompression. The decompressed ureterocele typically appears as a pseudomass or mucosal thickening.[126] A VCUG is performed 3 months later to demonstrate whether reflux has been created.

Partial Nephrectomy

The key to success with partial nephrectomy at any age, but especially in the infant, is complete and careful mobilization of the kidney. The vessels of babies are prone to spasms and intimal tears (Figure 40.49).[104] Undue traction must be avoided as the organ is gently cleared from the surrounding pararenal fat. It helps to intermittently discontinue the manipulation of smaller kidneys. In cases where vascular spasm persists, topical vasodilatory agents, such as papaverine, can be applied. The loss of small amounts of function is a common finding. A mean decrease of 6.8% occurred in 60 kidneys of children undergoing open partial nephrectomy in one series.[127]

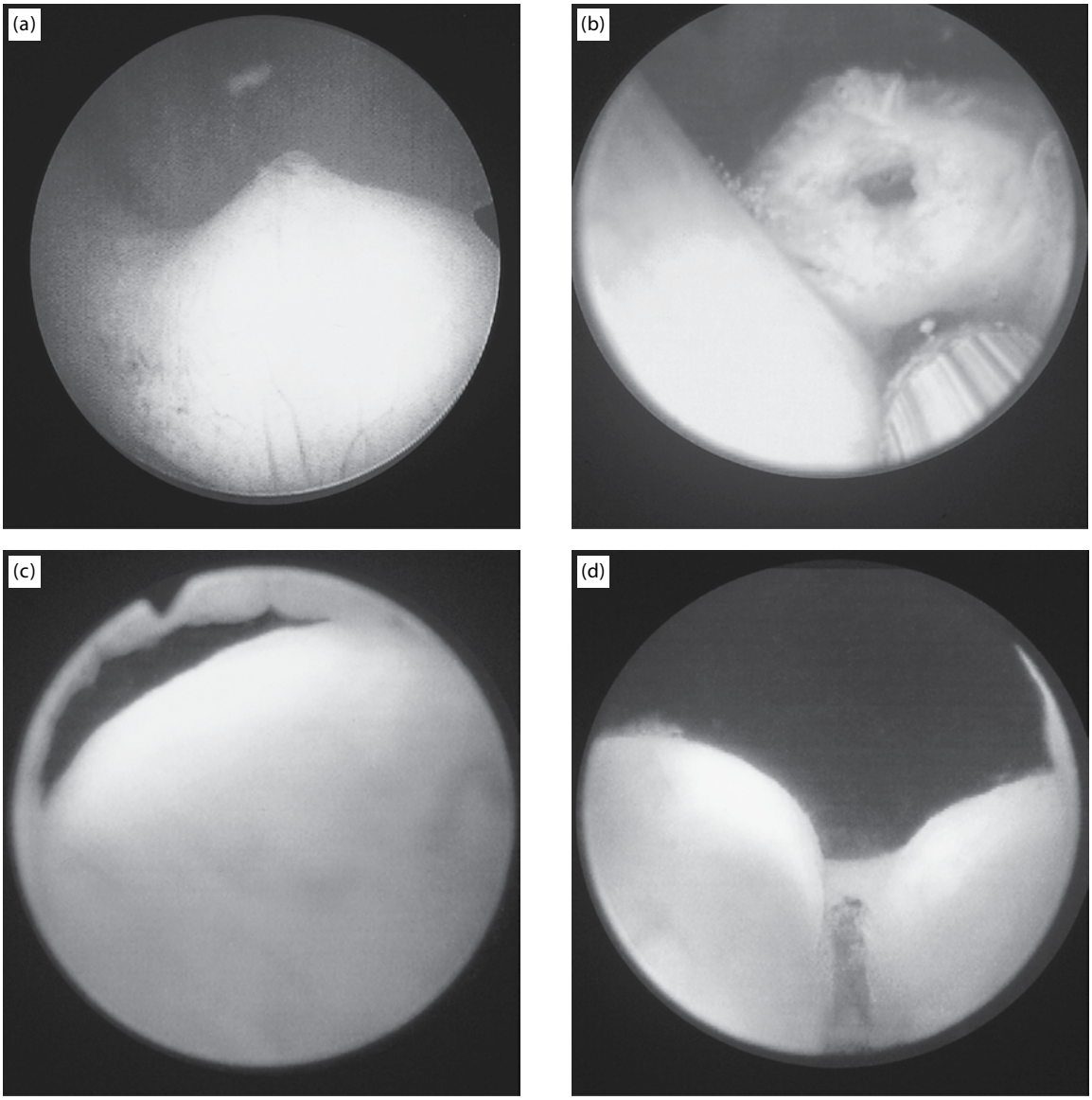


FIGURE 40.47 (a) Cystoscopic appearance of intravesical ureterocele. (b) The ureterocele is decompressed after incision by fine bugbee. (c) The extravesical ureterocele is seen occluding the bladder neck. (d) Wire applied at medial base with intent of preserving the flap valve effect.

In some cases, the vascular pedicle to the upper pole is isolated from that of the lower, making it easily discernable. In others, branching of the two occurs near the renal hilum, making identification of the upper-pole vessels more difficult. After the vessels are identified, vessel loops are placed around them. The ureter is transected at its midsection and mobilized superiorly, posterior to the anteriorly positioned renal vessels. Once freed, the ureter can be swung beneath the vessels and used as a handle on the upper pole, providing traction during its separation from the lower. Upper-pole blanching will occur after its vessels are ligated (Figure 40.50). Clamps on the lower vessels are avoided. Instead, the kidney is gently grasped between the thumb and index finger to help control bleeding. A rim of the renal capsule can be peeled off the upper pole and preserved to serve as reinforcement of the lower pole closure. The poles are then separated with cautery (high settings) along the line of vascular demarcation (Figure 40.51).

When a fish-mouthed defect remains in the lower pole, it can be closed with chromic mattress sutures that incorporate parenchyma and capsule. Otherwise, a flap of pararenal fat can be mobilized and tacked into position to cover the defect. Suturing the capsule of the remaining lower pole to the adjacent muscle is also recommended to avoid postoperative torsion. A drain is left in the renal fossa.

Ureteropyelostomy and Ureteroureterostomy

The principles of successful ureteropyelostomy and ureteroureterostomy are identical to those of

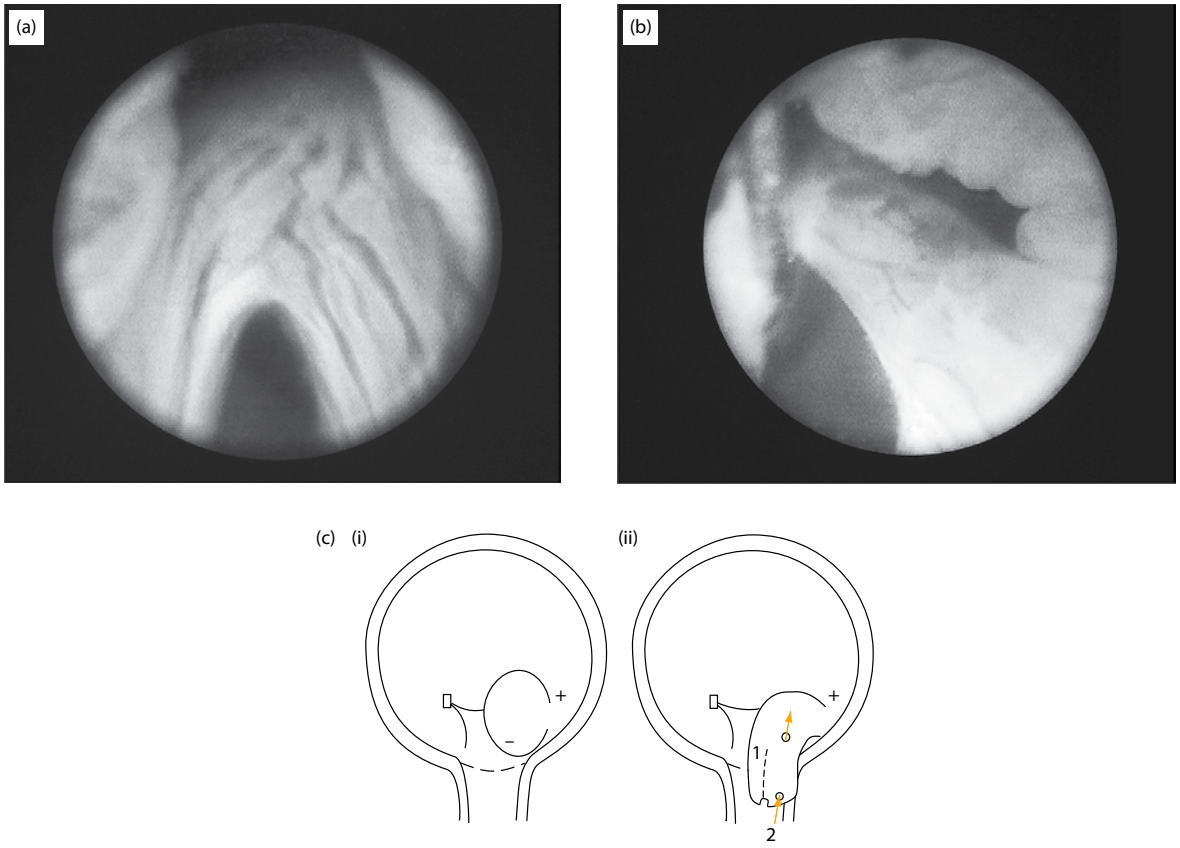


FIGURE 40.48 (a) Cystoscopic view of the sphincteric ureterocele having a widely open orifice (six o'clock position) distal to the bladder neck. (b) Vertical extension by wire eliminates the element of obstruction that accompanies the variant until definitive bladder reconstruction can be done at a later age. (c) The diagram depicts differences in incisions between intravesical ureteroceles (i) and sphincteric varieties (ii). (Adapted from Blythe B et al. *J Urol* 1993;149:556.)

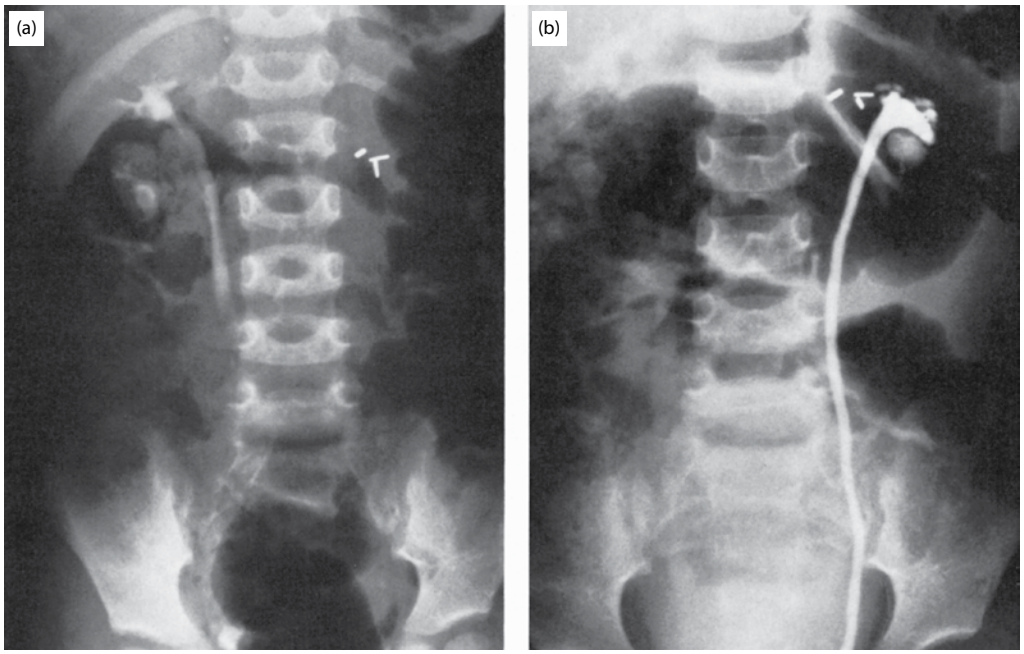


FIGURE 40.49 Vascular injury after left upper-pole heminephrectomy and partial ureterectomy. (a) After surgery, failure of contrast excretion by the remaining lower pole of the kidney, although the segment had been well vascularized prior to surgery. (b) A retrograde pyelogram demonstrates a shrunken unobstructed lower-pole moiety.

FIGURE 40.50 Mobilization is completed before excising the upper-pole segment. The ureter has been transected and carried behind the vessels to the lower pole of the kidney, providing a useful handle and guide to demarcation for heminephrectomy.

dismembered pyeloplasty: minimal handling of the ureters and maintenance of their orientation. Luminal disparity between the recipient collecting system and upper-pole ureter is rarely a cause for concern[128] (Figure 40.52). In most cases, the anastomosis is anteromedially positioned. Traction sutures define the extent of the ureterotomy or pyelotomy on the recipient ureter. An oblique incision of the donor ureter is marked to match. Running 6-0 polydiaxanone sutures are used to complete the repair. Urinary drainage tubes are unnecessary, although a drain is left in the region of the repair (Figures 40.53 and 40.54). When VUR is absent, ureteroureterostomy can also be completed through an inguinal incision using similar surgical principles. Concerns about residual hydroureteronephrosis and urinary stasis as a consequence of the "yo-yo" phenomenon appear to be unfounded.[129] A temporizing cutaneous ureterostomy is utilized in cases where the recipient ureter is felt to be too small.

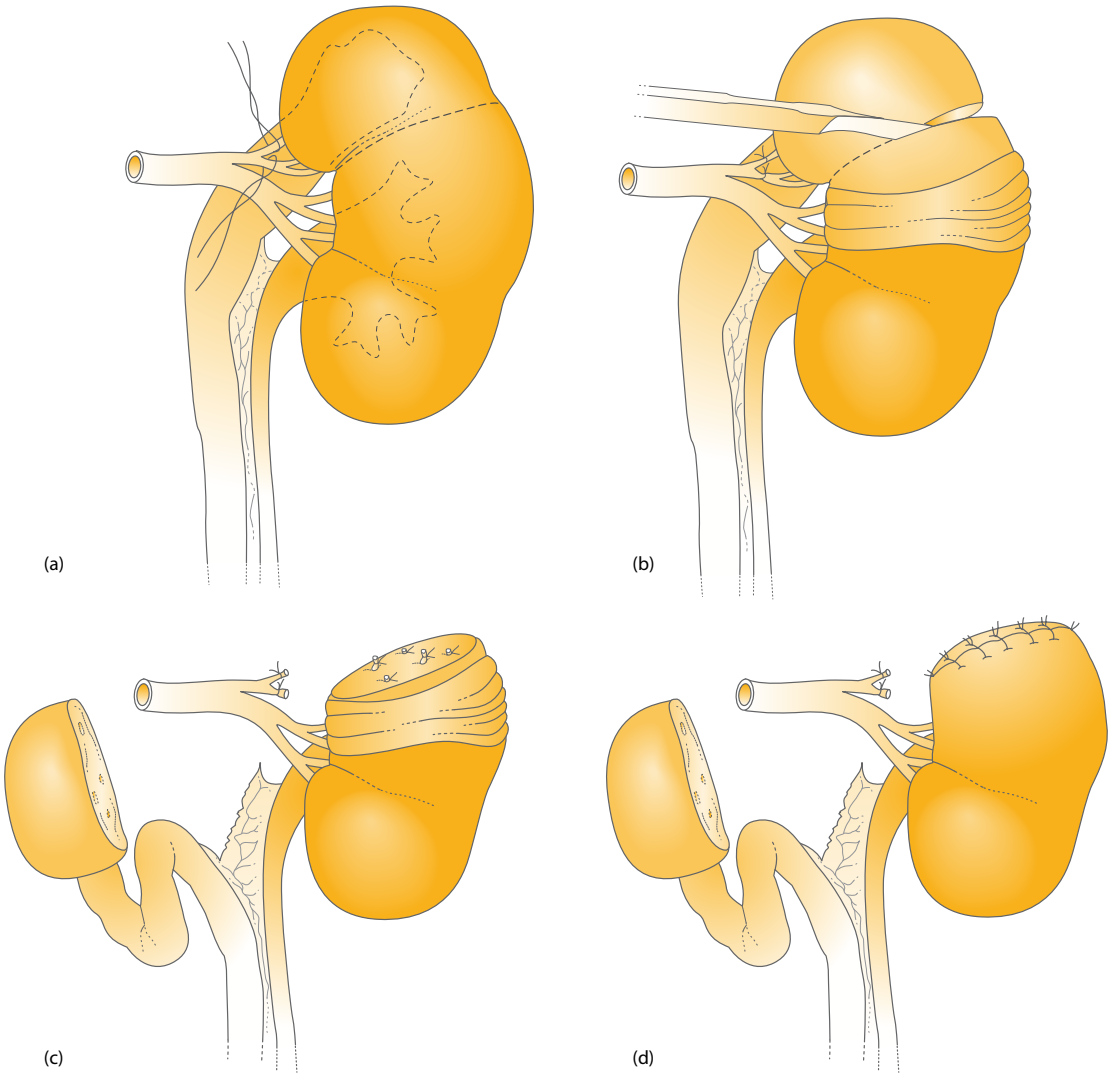


FIGURE 40.51 Technique of heminephrectomy. (a) Vessels to the upper pole are identified and ligated. At this point, the ureter can be fully mobilized from the area of the lower-pole hilum and swung posteriorly and superiorly. (b) The capsule is peeled away from upper pole and preserved for closure. A cautery offers less bleeding than the knife. (c) Significant vessels are ligated. (d) Closure incorporates the capsule and parenchyma.

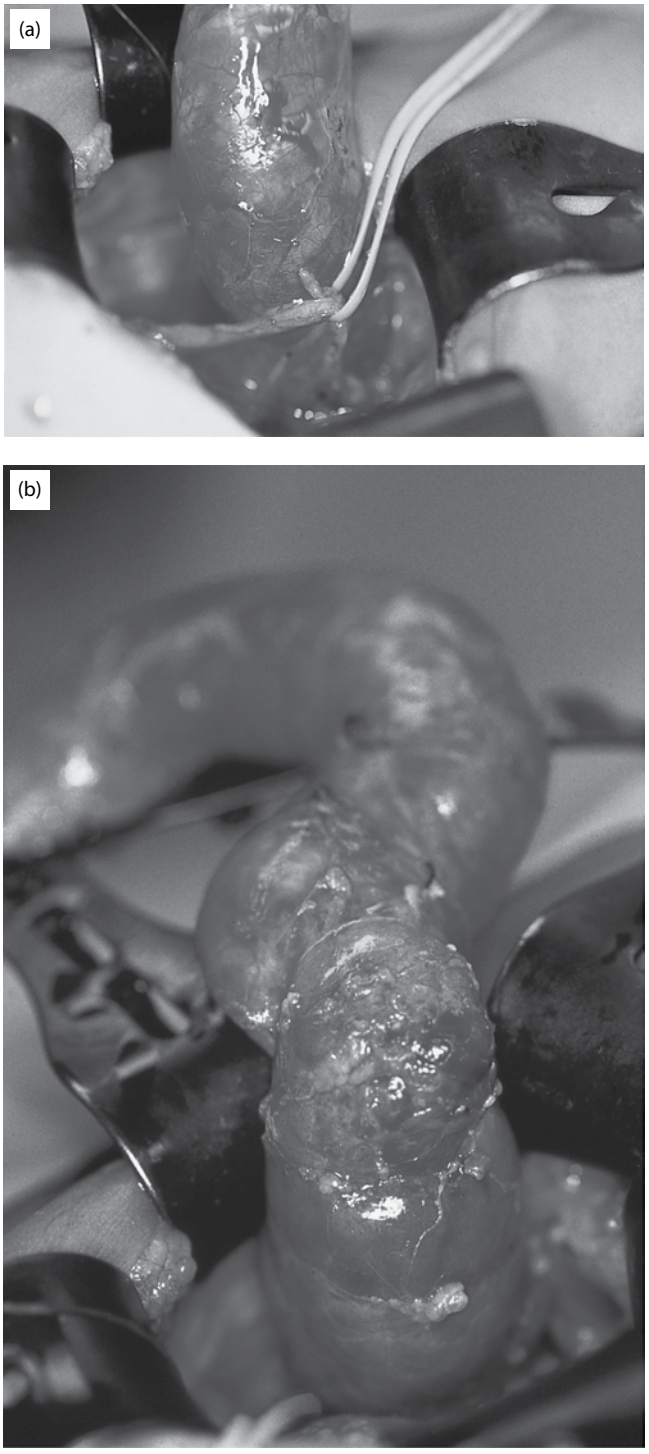


FIGURE 40.52 (a) Disparity in size between the obstructed ureter of the upper-pole moiety and the lower ureter (vessel loop) sometimes poses problems for ureteroureterostomy. (b) Since the upper pole shown grossly provided only moderate function, a heminephrectomy was performed.

Subtotal Ureterectomy

As much of the abnormal ureter as possible should be removed in concert with a heminephrectomy or renal salvage procedure. After dividing the ureter, a 12 F red rubber catheter is sutured within to provide traction during its dissection. The ureter to the lower pole is identified and minimally handled. Long, narrow retractors are used to lift away the peritoneum as the adventitia and periureteral tethers to the upper ureter are taken down with selective cautery. The dissection is ended near the level of the pelvic brim, where the ureters become more intertwined. Ligation is done with 00 or 000 polyglycolic acid suture after aspiration of the obstructed ureter.

Lower Ureterectomy

When a lower ureterectomy is necessary, a transverse Gibson-type incision is made along a lower abdominal crease. The obliterated hypogastric artery is identified and ligated. This is followed posteriorly until the ureter is encountered medially. The proximal portion of the ureter is pulled into the wound and acts as a handle during the remainder of the dissection. The ureter should be mobilized from within its adventitial sheath, avoiding the adjacent peritoneum and vas deferens. Once the mobilization is complete, the ureter is ligated and transected just outside the bladder. When urethral ectopy is being addressed, a catheter is placed to aid in the dissection. The ureter is mobilized to just above the pelvic floor, where it is ligated and transected. The distal insertion can be left alone and undue dissection of the sphincter avoided. In the case of duplication, the shared wall of the upper-pole ureter is left attached to that of the lower pole, avoiding damage to the blood supply. After resecting the ureter at the level of the bladder, several sutures are placed to obliterate its lumen at the hiatus (Figure 40.55).

Ureterocelectomy

The goals of this aspect of ureterocele surgery—removal of the ureterocele itself, correction of associated reflux, and repair of any bladder defect—can be achieved by a number of different approaches. A *transvesical approach* gives the best opportunity to assess the problems associated with the anomaly and to surgically respond accordingly.

The bladder is opened and the submucosal extent of the ureterocele is appreciated after incising its dome. Laterally and medially, the planes between the ureterocele lining and overlying bladder mucosa are better defined using fine cautery dissection. Some bladder mucosa should be preserved for coverage of the resultant defect. As the enucleation or excision is carried posteriorly, the ureterocele lining is excised by defining its plane with the underlying detrusor. Proximally, one or both ureters are circumferentially mobilized at their entrance to the bladder. Mobilization is identical to that of ureteroneocystostomy. Lumenal tailoring is usually necessary for the ureter associated with the ureterocele. The bladder defect that remains after the dissection is closed with interrupted sutures. Ureteral reimplantation is completed with ipsilateral advancement-type (Glen–Anderson) or cross-trigonal (Cohen) reimplantation techniques (Figure 40.56).

Distally, ceco- and sphincteric ureteroceles present a special challenge because of their urethral projections.

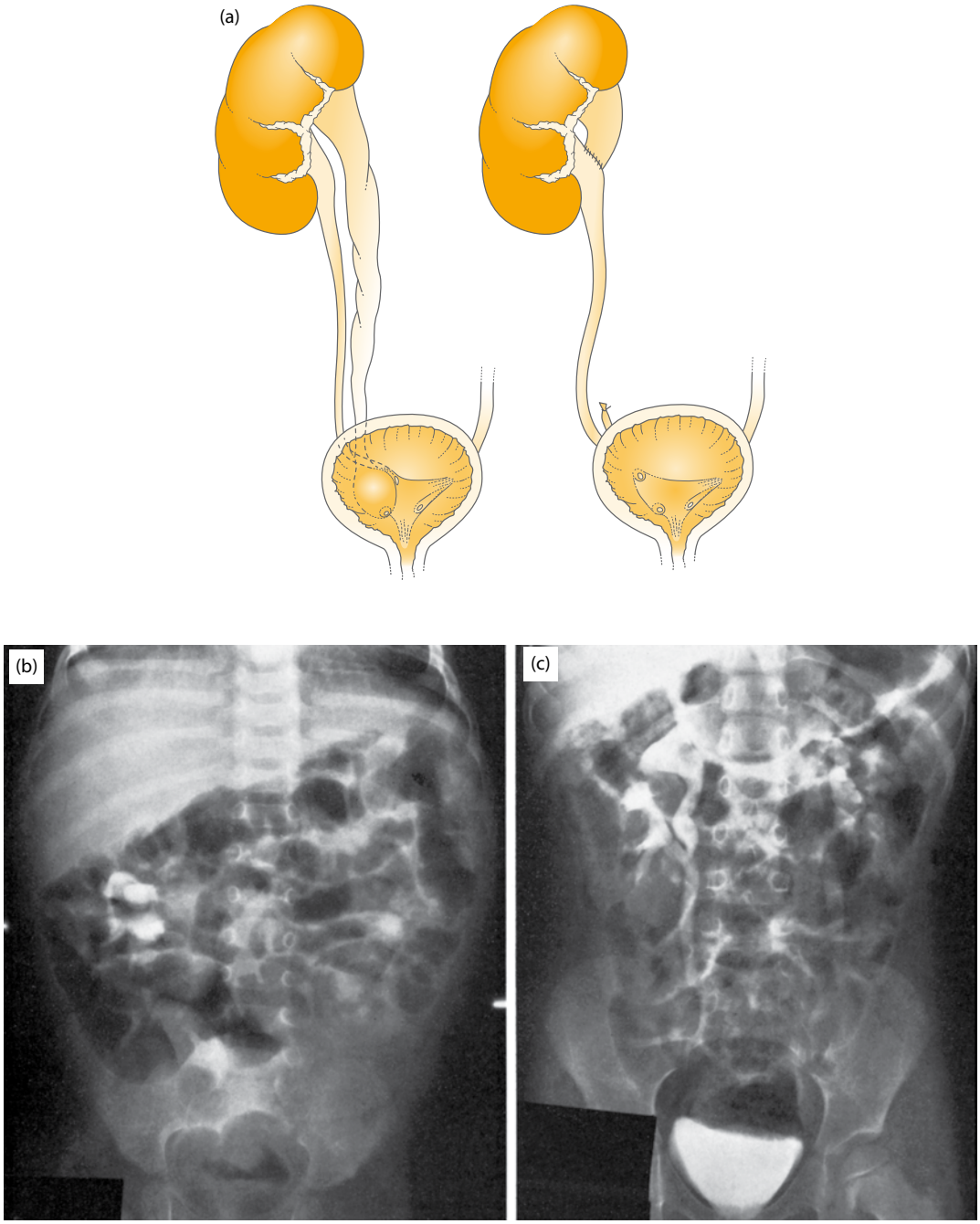


FIGURE 40.53 (a) Pyeloureterostomy and subtotal ureterectomy can be used to treat ureteroceles or ectopic ureters. (b) EU shows bilateral duplication and ectopic ureteroceles. A poorly functioning right upper moiety showed salvageable function by radionuclide scan. (c) An excretory urogram after the right pyeloureterostomy and left heminephrectomy shows return of function in the right upper segment and decompression of both ureteroceles below.

Flap valve obstruction of the bladder can result if tissue is left to balloon into the urethra during voiding.[131] However, extensive dissection should be discouraged to avoid damage to the sphincter mechanism. Instead, when the distal extent of the projection can be appreciated, it can be filleted open and its edges trimmed flush with the urethra. Otherwise, the opening to the projection can be defined and closed at the bladder neck, leaving the lumen intact where it rarely poses a problem. The efficacy of ureterocele excision and ureteral reimplantation with bladder reconstruction is shown by a series of 54 patients with ectopic ureterocele. After long-term follow-up (9.6 years), almost all patients were continent ($n = 51$). Ten required subsequent intervention for persistent VUR.[132] In cases where the detrusor muscle is attenuated, the overlying mucosa should be excised or fulgurated and the muscle plicated to shore up the defect.

Ureteroceles can be corrected by other approaches. *Marsupialization* has been successful in some cases, excising the intravesical outpouching of the anomaly and

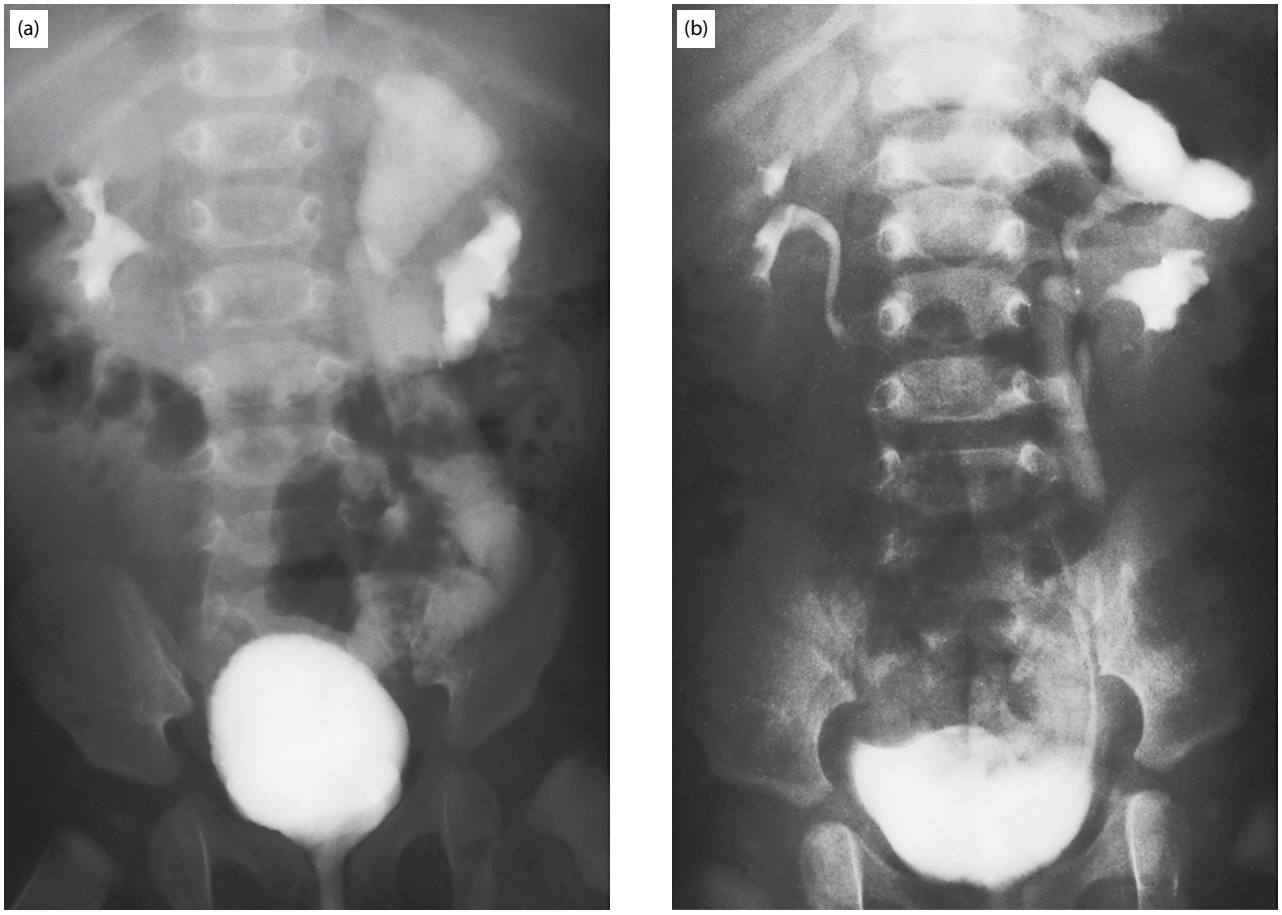


FIGURE 40.54 Nine-month-old female with intravesical ureterocele. (a) A preoperative excretory urogram shows good function to the upper pole. (b) Decompression of the upper pole after successful ureteroureterostomy.

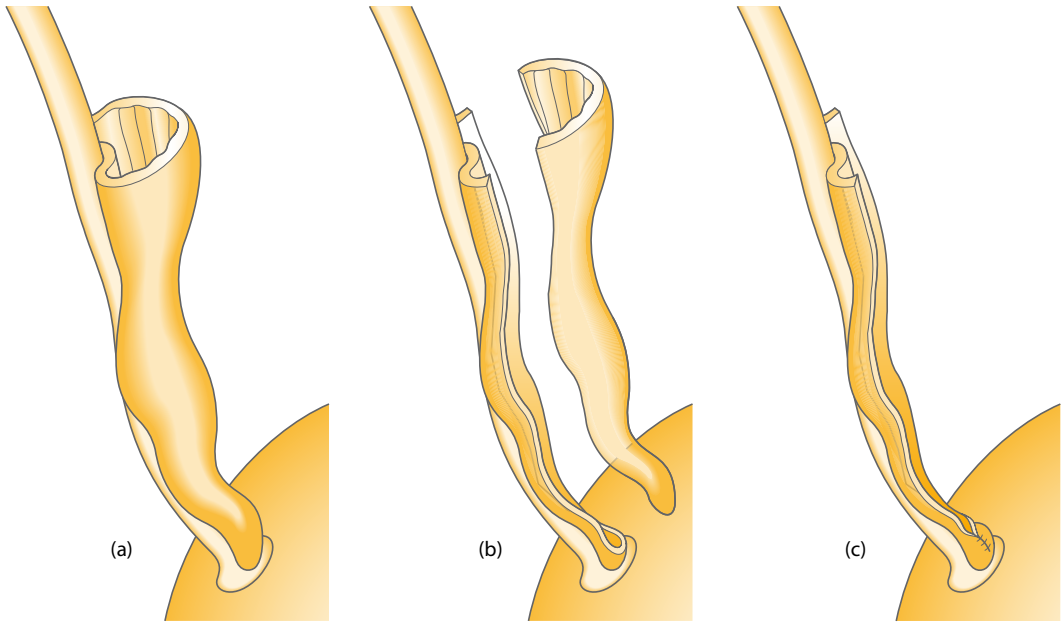


FIGURE 40.55 Lower ureterectomy. (a) It is often difficult to separate the two ureters as they near the bladder. (b) The outer wall of the dilated ureter associated with ectopia or ureterocele can be excised to the bladder, preserving a strip of common wall with the lower-pole ureter. (c) Transfixing sutures obliterate its lumen, with care being taken not to injure the orthotopic ureter. (Adapted from Schlussel R, Retik A. Anomalies of the ureter. In Walsh PC, Retik AB, Vaughan ED Jr, Wein AJ, eds., *Campbell's Urology*, 7th edn. Philadelphia: WB Saunders, 1998, 1820–9.

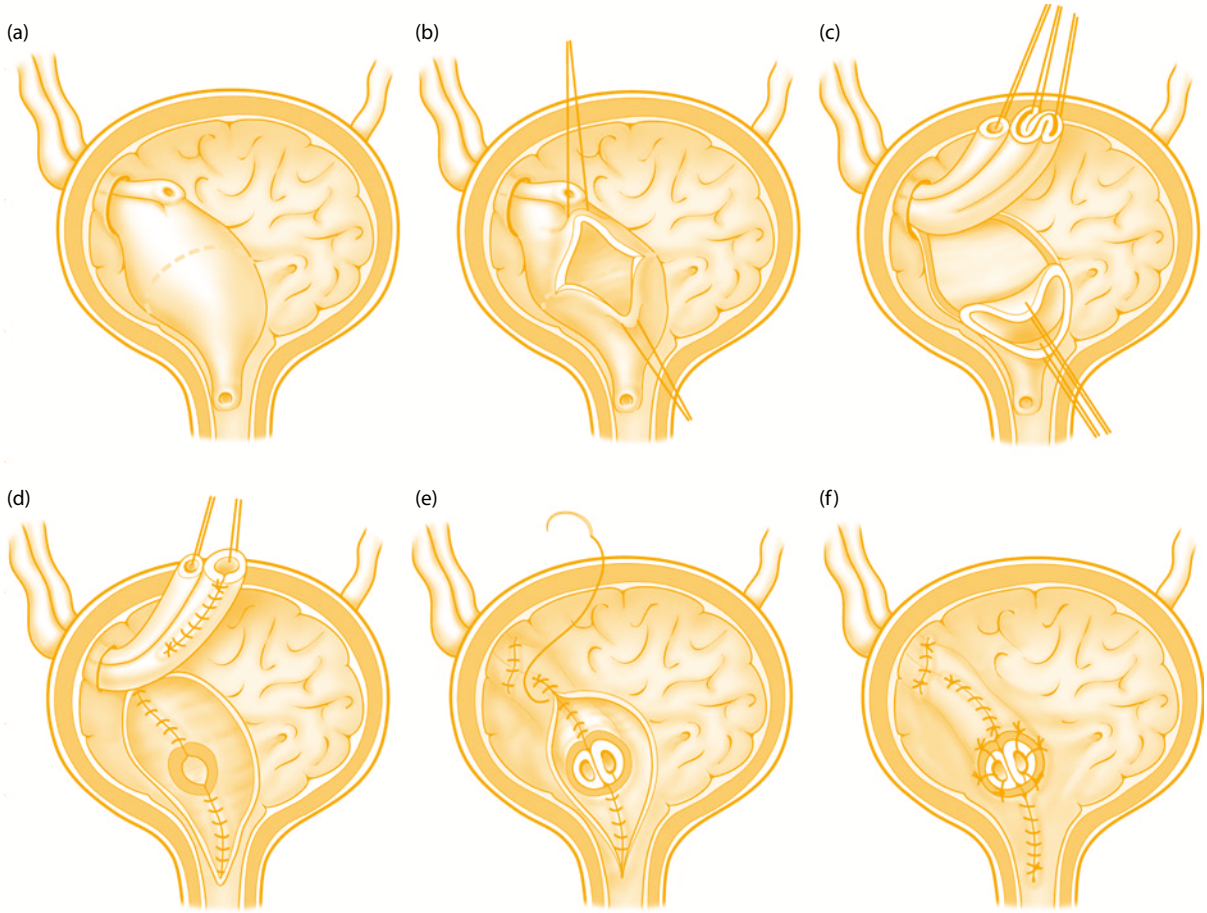


FIGURE 40.56 Technique for excision of ectopic ureterocele with common sheath reimplantation of both ureters. (a) Right-sided ureterocele. Contralateral ureter in close proximity. (b) Ureterocele can be opened transversely (as shown). A vertical incision can sometimes offer better visualization of the urethra. In many cases, the mucosa overlying the ureterocele is thinned out and must be discarded. (c) The posterior wall is incised and dissected away for underlying detrusor. The dissection is carried around to the bladder mucosal edges to enable complete removal of the ureterocele. Ureteral orifices are circumscribed and mobilized. (d) Ureteral mobilization completed. The dilated ureter tapered opposite the common wall. (e) Both ureters brought through the new hiatus in the bladder wall, although the cross-trigonal method can also be used. (Adapted from Schlussel R, Retik A. Anomalies of the ureter. In Walsh PC, Retik AB, Vaughan ED Jr, Wein AJ, eds., *Campbell's Urology*, 7th edn. Philadelphia: WB Saunders, 1998, 1820–9.)

leaving its back wall in continuity with the adjacent bladder as coverage (Figure 40.57).[105] Reimplantation can be done beneath the marsupialized ureterocele, although it is often necessary to create a trough by incising its mucosa, which is more intimately attached to the posterior musculature than in normal bladder. Marsupialization is probably less likely to cause sphincter damage than enucleation. To its detriment, the modification is unable to correct defects in the detrusor and/or sphincter, and thus is most applicable to smaller ureteroceles. In a multi-institutional study of 57 cases of complete excision versus marsupialization, no significant difference was seen in the clinical outcomes.[133]

Another approach is to address the ureterocele extravesically. This can be combined with a heminephrectomy or a distal ureteroureterostomy done through the same incision (Figure 40.58).[134] A portion of the ureterocele wall can be excised extravesically without opening the bladder mucosa and any significant detrusor defect closed. Reimplantation of an upper-pole ureter can also be successfully performed. The extravesical approach may lessen the chances of developing postmanagement bladder dysfunction, especially in children with unilateral variants.[135] Although less invasive, this approach cannot address the suburethral extensions found with some ureteroceles and does not provide a solution to the contralateral or ipsilateral reflux sometimes seen after correction of the anomaly.

Laparoscopy and Robotic-Assisted Management

Partial nephrectomies, ureterectomies, and reconstructive ureteral surgery can be done laparoscopically. Shortened hospitalizations and decreased morbidity are noted when compared with open procedures. Magnification also aids in the dissections.[136–140] Laparoscopy also provides another option in locating ectopic ureters associated with small dysplastic kidneys that cannot be identified

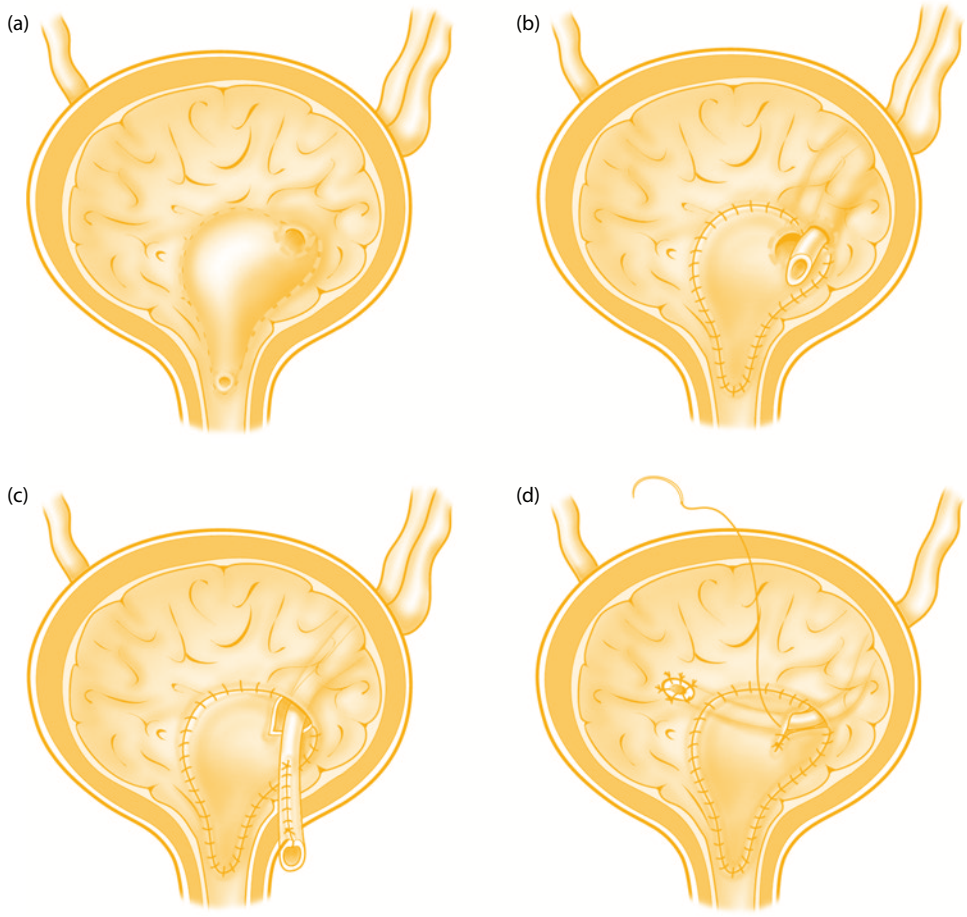


FIGURE 40.57 Marsupialization of ureterocele. (a) Ureterocele is incised at its junction with the normal bladder and sutured to mark edges and secure hemostasis. (b) Completed marsupialization. Mobilization of the duplex ureters is begun as a common sheath. (c) Ureteral mobilization is complete and the bladder defect from dissection is repaired. The dilated ureter has been excised (as shown) or can be tapered opposite the common wall. (d) Cross-trigonal reimplantation completed beneath the mucosa covering the original base of the ureterocele. (Adapted from Scherz HC et al. *J Urol* 1989;142:538.)

diagnostically.[141] Reports of increasingly larger groups of children treated with the so-called minimally invasive approach cite results that are comparable to the surgical outcomes offered by conventional open surgery.[142,143] The prolonged lengths of surgery cited in most reports are felt to be a concession to the learning curves required of the techniques early in the experience. And like open surgery, serious complications have occurred,[144] including loss of function of a lower-pole moiety after partial nephrectomy and urinoma formation.[145] Nevertheless, the role for laparoscopy in the management of duplication anomalies, as well other urologic anomalies, will only continue to expand.[146] In addition, robotic-assisted management of these anomalies, until now largely limited to adults, will undoubtedly extend to include children.[147,148]

POSTOPERATIVE CONCERNS

An ultrasound or functional study is obtained 6 weeks after surgery, depending on the procedure used to address the anomaly. The status of salvaged upper-pole kidneys or remaining lower-pole moieties and the effects of surgery on the bladder are assessed. Improvement in the degree of dilatation is to be expected of most patients, although residual hydronephrosis, the consequence of congenital obstruction, is a common postoperative finding. This typically improves with time.[149] Where concerns of obstruction persist, a nuclear renal scan is obtained. Voiding studies are performed 3–6 months after bladder construction to document the adequacy of the repair. Prophylactic antibiotics are continued in the interim. Children with complex urologic histories require periodic follow-up. The need for more prolonged serial radiographs depends on the remaining urinary configuration. In cases where the anomaly is presumably corrected, an ultrasound 2 and 5 years later is probably adequate. Primary physicians complete periodic checks of the urine, blood pressure, and interval somatic growth. Patients who remain at risk, because of persistent reflux, for example, require more frequent evaluation and, if necessary, secondary surgery.

Ureteroceles are particularly challenging in this regard. The length of an adequate trial of medical management

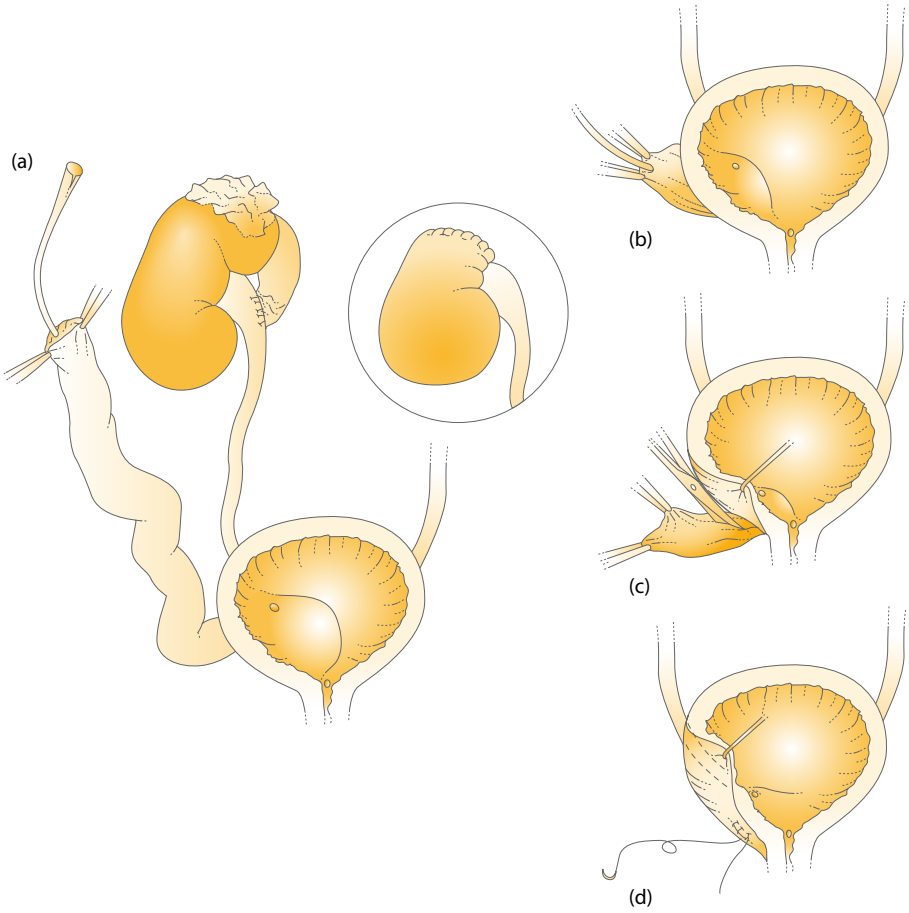


FIGURE 40.58 (a) The technique of extravesical ureterocele excision can be used after either upper-pole heminephrectomy or ureteroureterostomy. The remainder of the upper-pole ureter is cannulated and approached through the lower incision. (b and c) Extravesical dissection can be completed and the detrusor defect repaired (d). Both ureters can be detached to allow for easy separation of their common wall and the lower-pole ureter reimplanted using a Lich-type repair after repairing the detrusor defect.

for VUR that persists after an upper tract approach or selective incision has not been defined. Although spontaneous resolution of reflux associated with ureterocele occasionally occurs, it appears to do so at rates significantly lower than those seen with primary reflux. Most bladders are large enough to reconstruct as the child approaches his or her first birthday. Although it would seem preferable to address ureteroceles before the onset of toilet training, there may be no optimal age for surgery. In one series, bladder dysfunction appeared in 22 of 33 (67%) of patients whose ectopic ureteroceles were excised and bladders repaired at a mean of 10 months of age. Infrequent voiding, large capacities, and significant postvoid residuals were commonplace. The appearance of voiding dysfunction had no correlation with ureterocele size or location,[150] although children with bilateral ectopic ureteroceles may be particularly prone in this regard.[151] Whether these findings are surgically acquired or an inherent component of the anomaly is unclear. Similar rates of dysfunction in patients treated with upper tract surgery alone suggest a congenital component.[152] Regardless, the observation is an important one and may account for the lower rates of success with ureteral reimplantation in these children, when compared with ureteroneocystostomy for primary reflux. Bladder dysfunction should be considered a contributing factor in any child who continues to have persistent VUR after ureterocele surgery. Urodynamic testing and an assessment of bladder emptying should be obtained before considering any additional surgery.

RELATED CONDITIONS

Bilateral Single Ectopic Ureters

Bilateral single-system ectopic ureters are far more common in girls, who present with significant urologic problems as a consequence. The trigone and bladder neck is wide and poorly defined because of the aberrant insertions of the ureters. These usually drain into the distal urethra, although genital ectopy has also been described. Sphincter deficiency and bladder outlet incompetence result. The presentation is very similar to that in patients with epispadias. In addition, the bladder is typically small and the detrusor thin walled, in theory because it has never been required to store urine during development (Figure 40.59). Renal dysplasia or varying degrees of

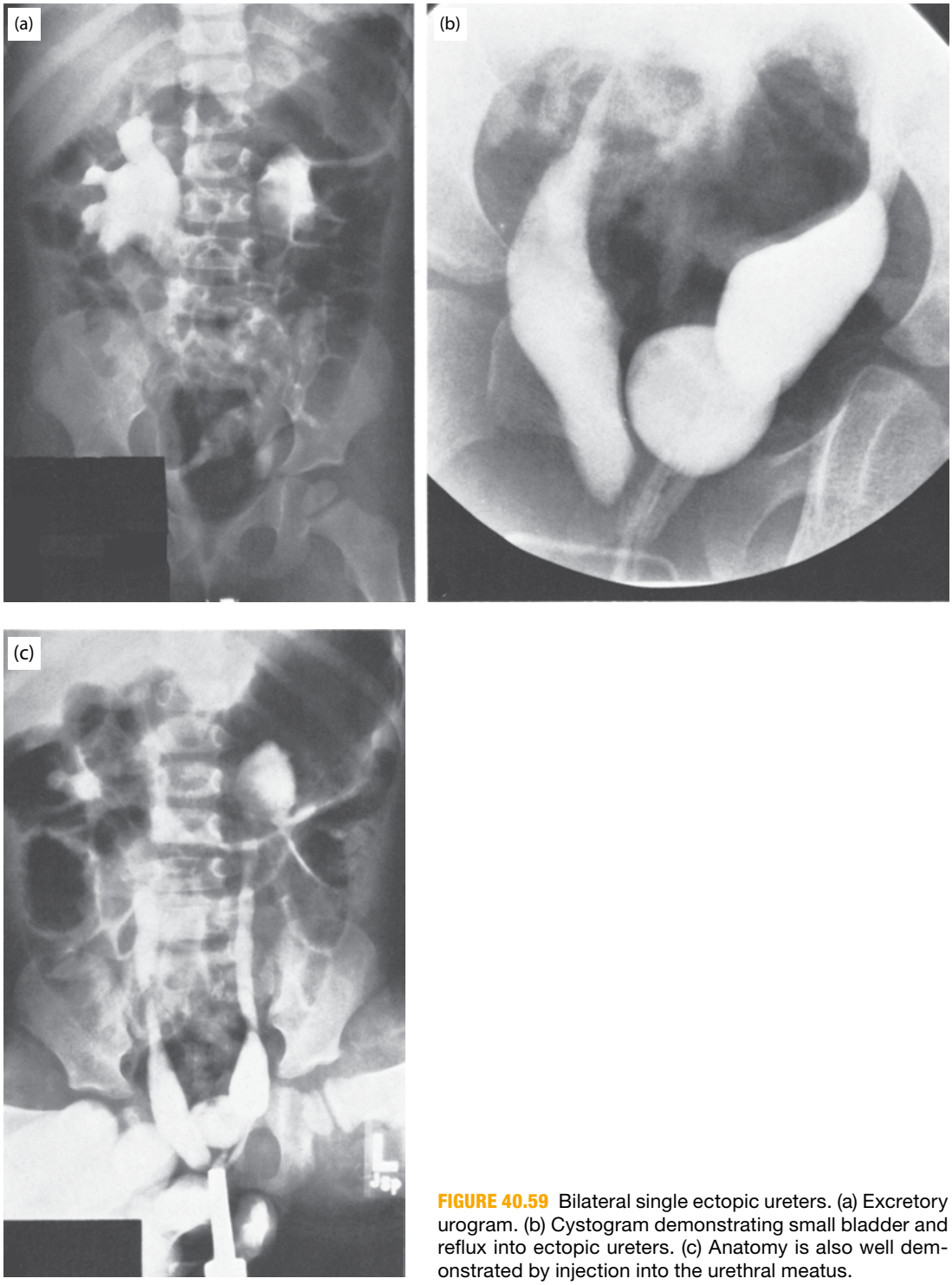


FIGURE 40.59 Bilateral single ectopic ureters. (a) Excretory urogram. (b) Cystogram demonstrating small bladder and reflux into ectopic ureters. (c) Anatomy is also well demonstrated by injection into the urethral meatus.

hydronephrosis are usually present. Reimplantation alone does not correct these glaring urodynamic abnormalities in most patients,[40] although there have been exceptions.[153] Augmentation cystoplasty is often required, and bladder neck reconstruction becomes necessary to increase outlet resistance. Boys are also occasionally affected by bilateral single-system ectopia, which inserts into the prostatic urethra. Bladder dynamics are more favorable, presumably because the better-developed external sphincter helps to retain the urine necessary to stimulate bladder capacity.[154]

Ureteral Triplication

Triplication of the ureter is one of the rarest anomalies in the urinary tract.[155] The individual takeoff of three ureteral buds from the Wolffian duct or the presence of two buds with early fission of one of the two accounts

FIGURE 40.60 Ureteral triplication.

for the variants of complete or partial triplications that have been described. The most common is a trifid configuration with all three ureters uniting and draining through a single orifice (Figure 40.60). Triplicate ureters are more common in females and occur more often on the left side. Common presentations include UTI and/or signs of ureteral obstruction. Ureteral triplications can be associated with ureteroceles, ectopia, and renal fusion anomalies.[156–158] The principles in management are similar to those of duplication anomalies.

Lower-Pole Ureteropelvic Junction Obstruction

Proximal ureteral obstructions occasionally involve duplicated ureters at the renal pelvic junction.[159] These almost always affect the lower-pole ureter. Because of their similarity, most problems that affect the ureters of single-system kidneys can affect the lower-pole ureters of duplications. The configuration and size of upper-pole ureters more closely mimic those of a calyx, making them much less prone to obstruction (Figure 40.61). Ultrasonography demonstrates lower-pole hydronephrosis in the absence of ureteral dilatation. Renal scintigraphy is used to assess function and document obstruction (Figure 40.62). When the lower pole is salvageable, its pelvis is anastomosed to the adjacent upper-pole ureter (pyeloureterostomy) (Figure 40.63). The remainder of the ureter is ligated above the bifurcation and discarded.

Yo-Yo Reflux

The phenomenon of yo-yo reflux remains poorly defined and its clinical implications unclear. Ureteral dilatation of bifurcated ureters was noted in 41% of cases in one series.[160] This raised the question of disordered peristalsis

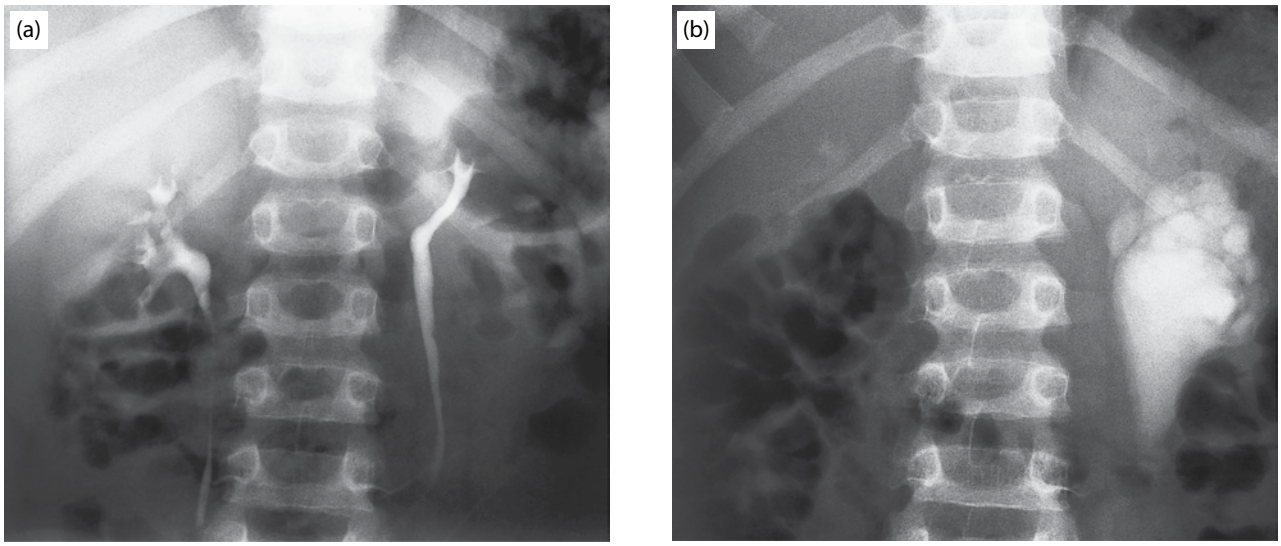


FIGURE 40.61 Difference in upper- and lower-pole configuration shown in different phases of an excretory urogram in a teenage boy with lower-pole ureteropelvic junction obstruction. (a) The early phase shows the upper pole with the appearance of a calyx. (b) The later phase shows the typical pelvic appearance of the lower pole. Note the kink form crossing the vessel.

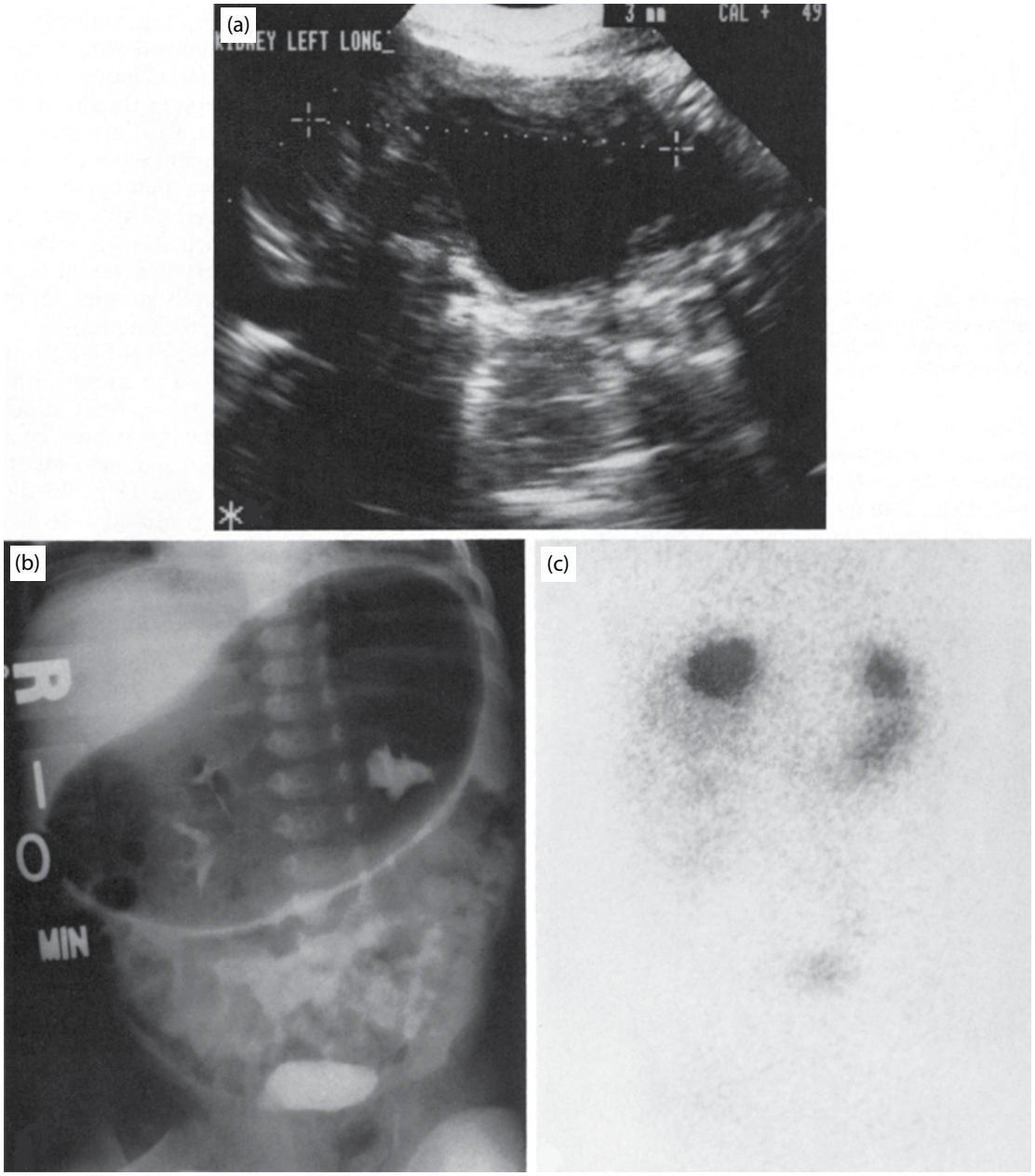


FIGURE 40.62 Lower-pole ureteropelvic junction obstruction diagnosed prenatally. (a) A renal sonogram demonstrates lower-pole hydronephrosis with better-developed renal parenchyma in the upper pole. (b) An EU shows opacification of the upper-pole structures on the left displaced superiorly and laterally. (c) A radioisotope scan demonstrates reduced but salvagable function in the left lower pole.

causing partial ureteral obstruction. In theory, antegrade peristalsis that begins in one ureteral limb initiates a reverse peristalsis in the other once it reaches the junction.[161] High-grade obstruction is rare, and an increased tendency to infections seems unlikely in most cases (Figure 40.64). In addition, despite altered to-and-fro peristalsis at its junction, the overall direction of urinary flow is still antegrade. In the rare patient in whom a clinically significant yo-yo is suspected, a high ureteroureterostomy is recommended, discarding as much of abnormal ureter as possible (Figure 40.65).[162] The preferred option for low-confluence bifurcations is to excise the shared segment and complete a common sheath ureteral reimplantation.

Remnant Ureters

A blind-ending branch of a bifid ureter is occasionally found in a child, although they are more often discovered in adults. These occur more commonly in females and on the right side. Most are associated with low-confluence bifurcations that are prone to reflux, although the anomaly can

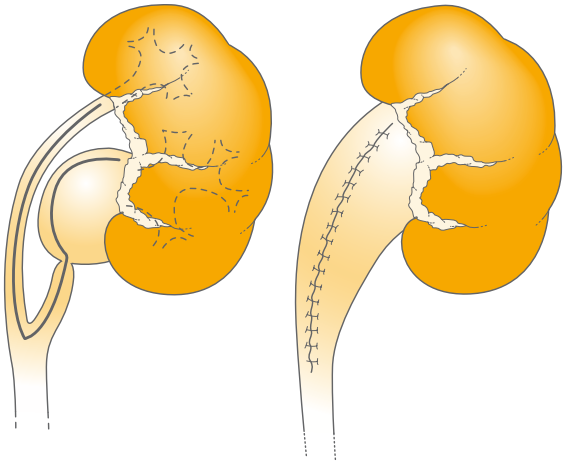


FIGURE 40.63 Surgical treatment of the lower-pole ureteropelvic junction obstruction in duplication. Joining two systems as shown brings less risk than attempting an isolated dismembered pyeloplasty of the lower system.

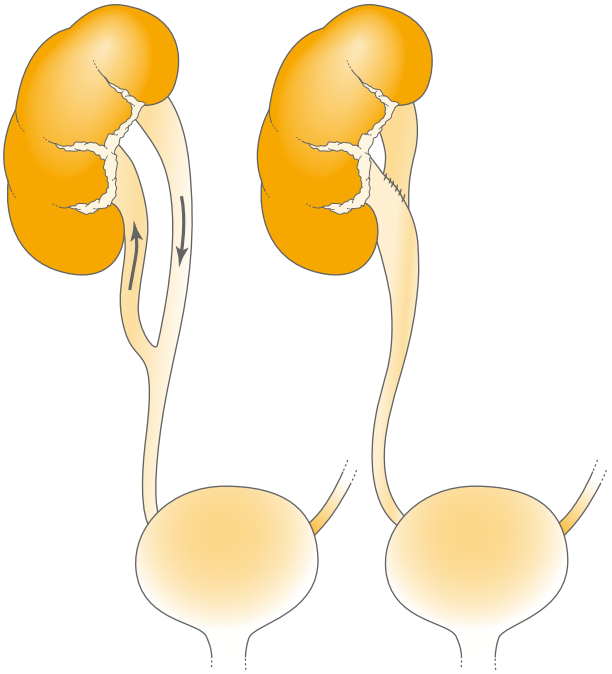


FIGURE 40.65 A high ureteropyelostomy with elimination of one limb of the yo-yo is occasionally required to treat ureteroureteral reflux.

also occur with complete duplications (Figure 40.66).[163,164] Proximally, the ureter ends blindly or may be associated with a small segment of poorly functioning kidney. For larger segments, excision is occasionally warranted. Otherwise, surgery is not indicated unless recurrent infections become problematic, in which case a common sheath

FIGURE 40.64 (a) Yo-yo reflux in a 2-year-old female may contribute to the mild dilatation of the two branches of the incomplete duplication shown. (b) An unusual duplication variant in a 4-year-old boy with lower-pole ureter ending as a saccular dilatation beneath the normal kidney. Although both children are possibly at risk from to-and-fro peristalsis, both are being followed expectantly and have done well.

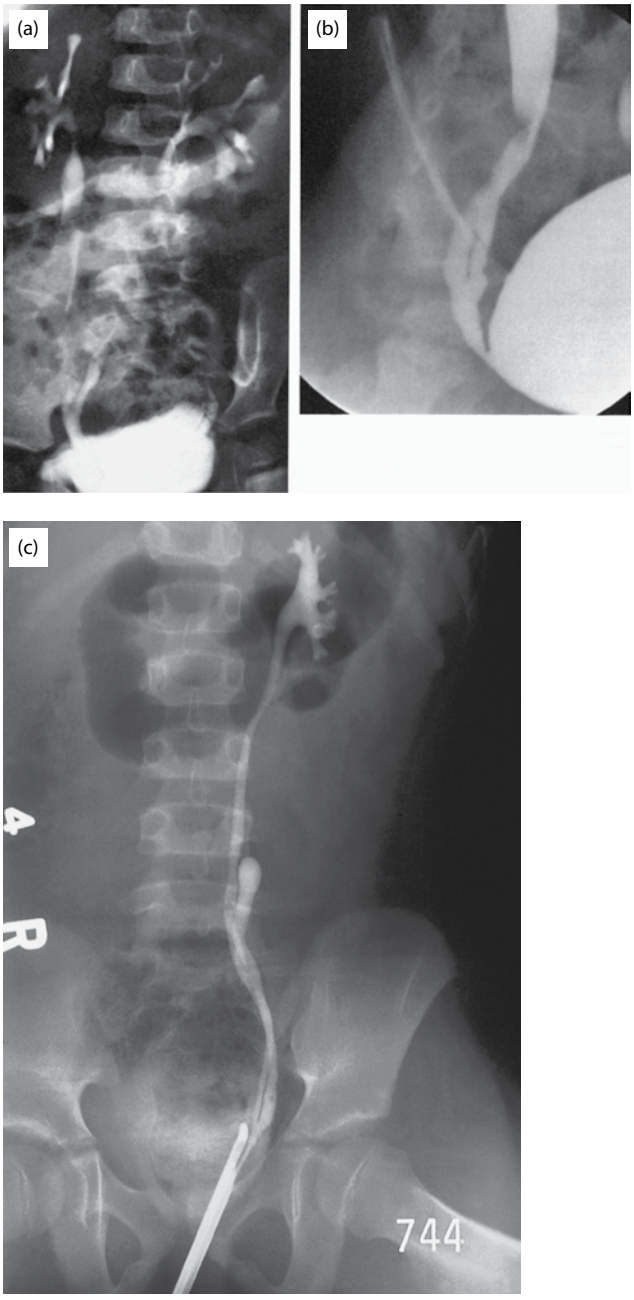


FIGURE 40.66 Blind-ending bifid ureter. (a) An excretory urogram outlines the blind-ending bifid ureter on the right side. (b) A voiding cystourethrogram shows reflux and bifurcation. (c) Retrograde study of similar abortive duplication whose orifice was seen at preoperative cystoscopy. When encountered unexpectedly, these can be safely reimplanted using a common sheath technique.

reimplantation is recommended. In occasional cases, an unsuspected duplication is discovered at cystoscopy or even during ureteral reimplantation. The ureter can be cannulated and a retrograde ureteropyelogram obtained. In nearly every case, the surgeon should still proceed with reimplantation unless the segment is short and easily excised. Complications from the retained renal parenchyma associated with remnant ureters have yet to be described.

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CHAPTER
41

Laparoscopic Management of Duplication Anomalies

Aaron D. Martin and Craig A. Peters

INTRODUCTION

The continued progression of laparoscopic techniques applicable to children has presented the opportunity of managing complex renal duplication anomalies using less invasive methods, without compromising surgical efficacy and safety. This chapter reviews the specific laparoscopic methods appropriate to the management of congenital duplication anomalies. Familiarity with the anatomic and functional implications of these anomalies, as well as of their appropriate evaluation, is presumed. The indications for laparoscopic correction of various duplication anomalies are the same as for open surgery. The principal determinants of the need for surgery, as well as the nature of the surgery needed, are the status of the affected renal moiety and the contralateral kidney and the presence or absence of reflux, obstruction, or incontinence. The options are upper- or lower-pole heminephrectomy, vesicoureteral reimplant, pyeloureterostomy, and ureteroureterostomy (U-U).

LAPAROSCOPIC OPERATIONS IN DUPLICATION ANOMALIES

In the setting of duplication anomalies, the most common operation performed is partial nephrectomy, predominantly of the upper pole. The usual indication to perform an upper-pole heminephrectomy is an upper pole with minimal or no demonstrable function. This is typically associated with a dilated corresponding ureter from distal obstruction, as in an ectopic ureter or ureterocele (UC), or incontinence from an ectopic ureter. In some ectopic ureters with incontinence, there is minimal to no dilation in the affected dysplastic upper pole. Laparoscopy provides excellent exposure to the hilum, and this particular operation is carried out more efficiently in laparoscopy than in open surgery.[1] The approach may be transperitoneal or retroperitoneal. The transperitoneal approach offers a wider operative field and is preferred for nephroureterectomy and when there is need for concomitant abdominal surgery (orchiopexy and ureteral reimplant); otherwise, the retroperitoneal approach is widely used. This may be in the prone or lateral position.[2–4] The instruments required are 5 or 3.5 mm cameras, scissors with cautery, a curved fine grasping or dissection instrument, a large grasping instrument for retraction, a clip applier (5 mm), an irrigating and aspirating device, and a harmonic scalpel or hook cautery. We have used 2 mm instruments, but now feel these do not provide adequate control.[2]

In the prone retroperitoneal approach, the patient is prone and the first incision is at the costovertebral angle (Figure 41.1). Blunt dissection is carried out until Gerota's fascia is exposed and entered. The retroperitoneal working space is developed using a balloon filled with saline. The balloon can be created from a finger of a surgical glove tied to a silastic catheter, or commercial devices are available. Developing the retroperitoneal space is accomplished with volumes from 90 mL in an infant to 150 mL in a school-aged child. After removal of the balloon, the first trocar is placed, secured, and insufflated to about 12 mmHg for school-aged children and 8 mmHg for infants. The surgeon is positioned at the ipsilateral side of the patient (affected kidney) or at the feet of the patient in smaller children. Secondary ports are placed under direct vision above the iliac crest lateral to the sacrospinalis muscle and at the posterior axillary line (Figure 41.1). The prone approach offers excellent exposure of the hilum with less concern for inadvertent pneumoperitoneum (Figure 41.2).

The lateral retroperitoneal approach (Figure 41.3) provides easier access to the distal ureter. However, it requires extensive mobilization of the peritoneum and retraction of the kidney for optimal exposure of the hilum.[5] The patient is positioned in the flank position, and the first incision is made at the lower border of the 12th rib. The working space is developed similarly to the prone approach, and accessory ports are placed one finger width from the top of the iliac crest and posteriorly in front of the lumbosacral muscle. Alternatively, they can be placed in a fashion similar to that of the prone approach.[6,7]

In the transperitoneal approach, the patient is supine and the first trocar is placed at the umbilicus with the open technique and secured in place. Two additional ports are placed under direct vision, one in the midline between the umbilicus and the xiphoid process and one in the midclavicular line in the lower quadrant (Figure 41.4). A fourth port for liver retraction may be placed at this time for a

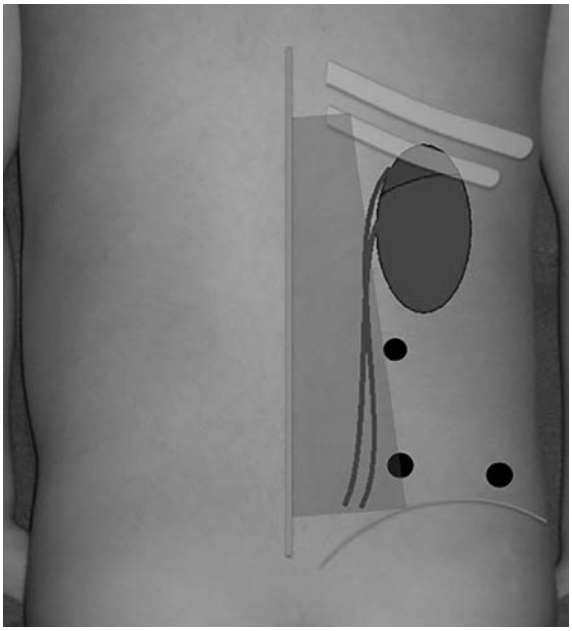

FIGURE 41.1 Port placement for prone retroperitoneal partial nephrectomy. The camera is usually placed in the port at the costovertebral angle.

right-sided operation. The table is then rotated so that the patient is in an oblique position, which allows the bowel to fall out of the operative field. Access to the retroperitoneum and kidney begins with mobilization of the right or left colon.[8]

Once access to the retroperitoneal space is obtained, the lower pole of the kidney is identified and mobilized until the two ureters can be identified. It is preferable to gain control of the hilum as soon as it may be adequately

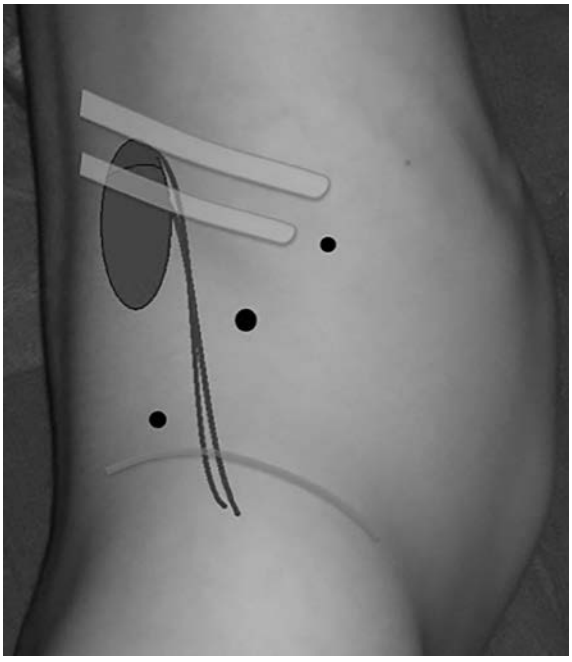

FIGURE 41.2 Port placement for the lateral retroperitoneal approach to the kidney.

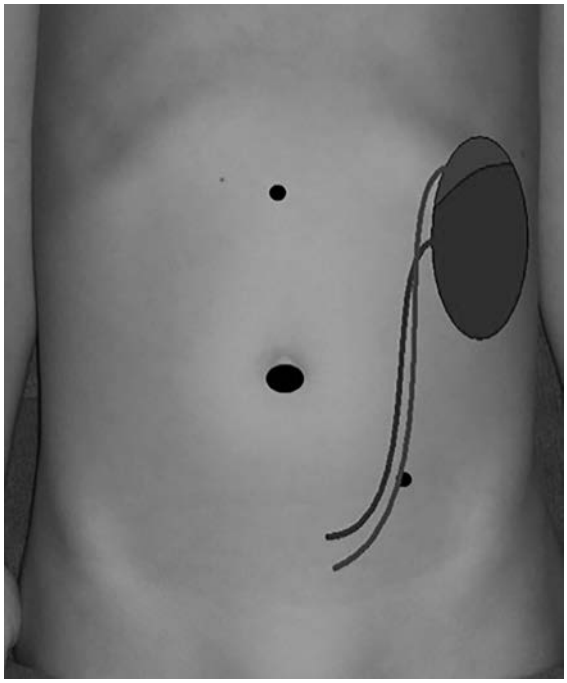

FIGURE 41.3 Port placement for the transperitoneal approach to the kidney, which provides excellent access to the distal ureter when this must be resected.

visualized. In the prone position, the kidney tends to fall laterally and anteriorly, exposing the vascular pedicle. The appropriate polar vessels are identified and clipped individually using a 5 mm clip applier. With the patient prone, the artery comes first in view and is taken first (Figure 41.2). Two clips are used on the proximal side and one on the distal end. Alternatively, a harmonic scalpel can be used if the vessels are small in caliber. Subsequently, the corresponding ureter is mobilized, transected just below the lower pole, and used as a handle to facilitate isolation of the corresponding pole. Occasionally, mobilization of the ureter is required prior to obtaining complete visualization and control of the vessels. Transection of the renal

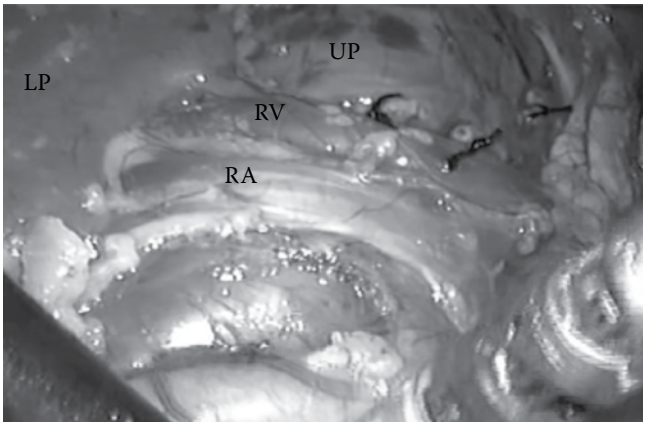

FIGURE 41.4 Exposure of the renal hilum and lower-pole (LP) renal vessels (RA, RV) during robotically assisted partial nephrectomy. The markedly dilated upper-pole collecting system is indicated (UP) passing posterior to the vessels.

parenchyma is then carried out with the harmonic scalpel or with the bipolar cautery.[9] The remainder of the ureter is then dissected away from the remaining ureter by staying very close to the ureter being removed to avoid devascularization of the remaining ureter. The distal ureteral stump should be suture ligated when reflux is present. In the ectopic ureter with both obstruction and reflux, usually those entering the bladder neck, the entire ureter should be removed and the defect closed with sutures. The specimen is removed from the largest port incision. Large cysts in dysplastic upper poles may need to be aspirated before the specimen can be removed.

The typical indication for lower-pole heminephrectomy in duplicated anomalies is a severely compromised lower pole as a result of high-grade vesicoureteral reflux (VUR) or, less often, severe ureteropelvic junction (UPJ) obstruction. The procedure can be undertaken transperitoneal or retroperitoneal, and prone or lateral, in a fashion similar to that of an upper-pole partial nephrectomy. It is best to expose the entire hilum first in order to positively identify the lower-pole vessels. In lower-pole partial nephrectomy, the plane between the upper- and lower-pole pelves is not as distinct and may be difficult to develop. Also, the calices of the dilated lower pole often protrude into the upper pole and may be entered during separation of the two moieties. All remnants of the calices and parenchyma must be removed in order to prevent formation of a urinoma (Figure 41.5). If the upper-pole collecting system is inadvertently entered, suture closure is recommended, as well as drainage. Removal of the lower pole through the initial incision may require morcellation.

RESULTS OF LAPAROSCOPIC PARTIAL NEPHRECTOMY

Table 41.1 shows the results of several series of pediatric laparoscopic partial nephrectomies. In general, the operative times are acceptable and the conversion rate to open surgery is low. In comparative studies of transperitoneal and retroperitoneal approaches, there is a minimal difference in times or outcomes. In studies comparing laparoscopic and open approaches, there is typically a shorter hospital stay, less blood loss, and less postoperative analgesic use with comparable outcomes.[4,10–15] Even in the infant, laparoscopic approaches for complex renal surgery are both safe and efficient.[12,13]

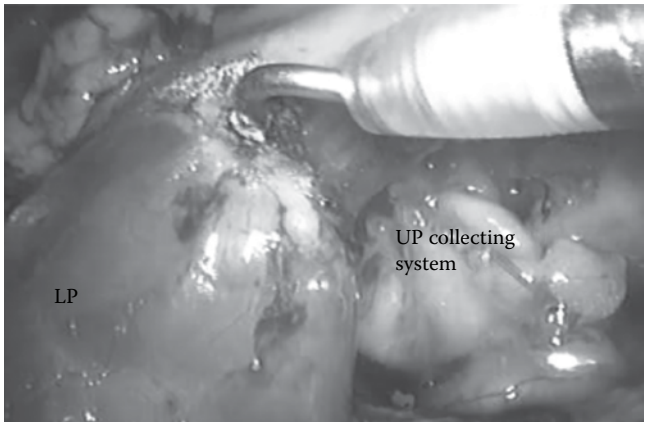

FIGURE 41.5 Transection of margin between the upper (UP) and lower (LP) poles during robotically assisted partial nephrectomy. The plane between the upper-pole collecting system has been developed to facilitate exposure of the thin connection that is being cut with cautery.

COMPLICATIONS

Possible intraoperative complications of laparoscopic partial nephrectomy include bowel, liver, and spleen injuries; abdominal wall vessel injuries; and vascular injuries.[16] On the right side, the duodenum can be injured while exposing the upper pole. It is important to recognize that what looks like the renal vein may in fact be the vena cava if proper orientation of the camera is lost. It is important to briefly reorient oneself prior to any definitive clip placement. Arterial injuries require prompt control of bleeding and repair. Conversion to open surgery may be necessary, depending on the severity of the injury and the experience of the surgeon. Although there is less need to manipulate the remnant pole during a laparoscopic partial nephrectomy, the possibility of arterial spasm in the remnant pole must be recognized and anticipated. This is more likely in infants, but can occur at any age. Any tension on the remnant pole vessels should be released and a syringe of papaverine prepared. If the affected pole does not "pink up," 0.5 mL of papaverine should be forcefully squirted at the affected artery. If no effect is seen, a second bolus of 0.5 mL should then be instilled. Alternatively, lidocaine (without epinephrine) may be useful to correct the vasospasm. Several recent series have reported loss of the lower pole with laparoscopic heminephrectomy, and it is unclear if this represents part of the learning curve or a specific risk.[17] Postoperative complications have been limited to urinoma formation, although none have been clinically significant. Simple aspiration is usually associated with rapid recurrence. If there is concern about a remnant pole leak, a double-J stent may be placed for several weeks. We have not seen any long-term problems with these and have usually simply observed them without untoward outcomes.

URETERAL SURGERY ASSOCIATED WITH DUPLICATION ANOMALIES

Laparoscopic vesicoureteral reimplant has limited indications in duplication anomalies. Isolated VUR of the lower pole is best managed by ipsilateral U-U. If the upper pole is also refluxing, typically as a result of previous incision of a UC, a common sheath reimplant is appropriate. An isolated lower-pole reimplant is considered when the upper moiety has been previously removed. In unilateral cases, simple or common sheath reimplant can be accomplished laparoscopically with a Lich–Gregoir extravesical reimplantation.[18]

For ureteral reimplantation, the patient is positioned supine, and ports are placed at the umbilicus and

TABLE 41.1 Summary data for laparoscopic partial nephrectomy in children, with conversion rates to open surgery

First author	Year published	No. of patients	Operative time (hours)	Length of stay (days)	Conversions to open	Conversion rate (% of total)	Approach
Janetschek[32]	1997	14	3.75	4.4	0	0	Transperitoneal
Yao[33]	2000	6	3.75	1	0	0	Transperitoneal
Borzi[5]	2001	17	1.3	NR	2	11.8	Retroperitoneal
Horowitz[34]	2001	14	1.66	2.6	0	0	Transperitoneal
Robinson[35]	2003	11	3.33	1	0	0	Transperitoneal
Valla[36]	2003	24	2.66	3.4	3	12.5	Retroperitoneal
Lee[10]	2005	14	3.2	1.7	0	0	Retroperitoneal
Sydorak[37]	2005	7	2.98	2.4	0	0	Transperitoneal
Wallis[17]	2006	26	2.9	2.2	4	15.4	Retroperitoneal
Castellan[38]	2006	32/16	2.08/2.22	2.6/2.3	0/1	0/6.25	Transperitoneal vs. retroperitoneal
Piaggio[11]	2006	14	3	2	0	0	Transperitoneal
Mushtaq[39]	2007	48	1.75	NR	0	0	Retroperitoneal
Chertin[12]	2007	10	NR	2.7	1	10	Transperitoneal
Leclair[40]	2008	48	2	3	10	21	Retroperitoneal
Fuchs[13]	2009	18	1.93	NR	0	0	Transperitoneal
Singh[41]	2010	42	1.5	NR	1	2.4	Retroperitoneal
Nerli[42]	2011	29	1.57	3	0	0	Transperitoneal
Pearce[43]	2011	8/16	3.14/2.56	2.62/2.56	3/7	37/44	Transperitoneal vs. retroperitoneal
Choi[14]	2011	30	2.98	1.56	0	0	Retroperitoneal
Esposito[44]	2015	102	2.6/4.1	3.5/4.1	0	0	Transperitoneal vs. retroperitoneal
Totals/ Average		**444**	**2.51**	**2.41**	**32**	**7.21**	

Abbreviation: NR, not reported

symmetrically in the midclavicular lines. Their level is determined by the size of the patient, being above the umbilicus in infants and below in the older child. The ureter is exposed by incising the peritoneum behind the bladder, permitting mobilization. A hitch stitch is placed to hold the bladder anteriorly to aid exposure. A detrusor incision of 3.5–4 cm is made with the hook cautery to permit creation of a submucosal tunnel for the ureter. The muscle is then brought around the ureter with interrupted sutures. No ureteral stenting is required. In bilateral cases, a laparoscopic intravesical approach can be used; however, urinary retention is rare with laparoscopic bilateral extravesical reimplantation compared with the open approach.[19,20] Laparoscopic UC excision has also been described, including extravesical reimplantation of the remnant ureter.[18]

In the case of an ectopic or obstructed upper pole with reasonable function, an ipsilateral U-U can be performed at the lower pole of the kidney or at the pelvic brim, assuming the lower pole is nonrefluxing.[21] For proximal U-U, which is generally useful when one ureter is markedly larger than the other, the positioning is identical to that for a lower-pole partial nephrectomy. For a distal U-U, the ports are placed similarly to those for a ureteral reimplantation and the ureters are exposed at the level of the pelvic brim. The donor ureter is transected obliquely with a length matching an incision in the recipient ureter. Running anastomosis is performed, and the ureters are stented only in the recipient ureter. In some clinical scenarios, it is more efficient to perform a U-U, even when there is little to no function of the associated upper pole, as the procedure is simpler and there is little risk to the remnant pole if well drained.

Associated lower-pole UPJ obstruction is best treated by creating a wide anastomosis between the lower-pole pelvis and the upper-pole ureter (pyeloureterostomy). On occasion, however, an isolated lower-pole dismembered pyeloplasty can be considered. This can be performed transperitoneally or retroperitoneally.[22] Ports are placed as in a transabdominal partial nephrectomy, but the retroperitoneal space can be exposed through a transmesenteric incision. The operation is carried out as an open

TABLE 41.2 Summary data for robotically assisted partial nephrectomy in children, with complication rates

First author	Year published	No. of patients	Operative time (hours)	Length of stay (days)	Complications	Complication rate (% of total)	Approach
Lee[27]	2009	9	4.5	2.9	1 (cyst/urinoma—no Sx)	11	Transperitoneal
Mason[30]	2014	21	5	1.5	6 (cyst/urinoma—no Sx)	29	Transperitoneal
Malik[45]	2016	16	2.25	2	6 (cyst/urinoma—no Sx)	38	Transperitoneal

Abbreviation: Sx, symptoms

dismembered pyeloplasty, with resection of the stenotic segment, spatulation of the ureter, and reanastomosis. A double-J internal stent is left in the repaired ureter. This operation requires significant skill in laparoscopic suturing and knot tying. For this reason, it can be more efficiently accomplished by using the da Vinci robotic surgical system (Intuitive Surgical, Sunnyvale, California).[23–25]

ROBOT-ASSISTED LAPAROSCOPY FOR DUPLICATION ANOMALIES

The use of robotics potentially expands the number of laparoscopic cases, enabling surgeons with limited laparoscopic experience to perform complex laparoscopic reconstructions requiring extended suturing skills. The da Vinci robotic surgical system is composed of three main parts: the robotic unit, with three (or four) robotic arms that hold the camera and instruments; the video–insufflation–light source unit, as in conventional laparoscopy; and the remote console, from where the surgeon controls the robotic arms.[26] It is equipped with a three-dimensional camera. The instruments presently available are 8 and 5 mm in diameter, the larger ones permitting the greatest maneuverability and options. Robotic laparoscopy presents significant advantages in terms of visualization, fine suturing capabilities, accuracy, and speed of surgery over freehand laparoscopy. In the small child, care must be taken in terms of patient preparation and positioning, setup, and port placement, yet renal surgery has been performed safely in children as small as 5 kg. Extravesical ureteral reimplantations, pyeloplasties, U-Us, and partial nephrectomies have been performed robotically in children.[27–29] In pyeloplasties and partial nephrectomies, the approach is typically transperitoneal, as retroperitoneal access can be difficult due to increased space needs for the robotic arms. For renal surgery, the robot is brought in from the side and angled from the shoulder. To perform a ureteral reimplant, the robot is brought in from the feet of the patient. Port placement is identical to that described above for laparoscopic transperitoneal surgery. While the surgeon sits at the console, the assistant will remain scrubbed at the patient's side, taking care of instrument changes. With the da Vinci robot, current instruments include a hook cautery, scissors, Debakey forceps, larger grasping forceps, two sizes of needle holder, and an articulated suction–irrigation device. These instruments are integrated with conventional laparoscopic clip appliers, irrigation and aspiration devices, scissors, and graspers. Dissection is carried out mostly with the hook cautery, as is the parenchymal resection in a partial nephrectomy. Vessels are clipped with a traditional clip applier maneuvered by the assistant. For a partial nephrectomy, it is recommended that the renal defect be closed, as was typically done with open surgery (Figure 41.6), to limit the risk of development of a urinoma, although these are rarely clinically problematic (Table 41.2).[30] The operations are carried out as previously described. Operation times are usually reduced, compared with conventional freehand laparoscopy, although overall time may be equal due to the preparation and docking time required with the robot. This time can be greatly reduced by training a dedicated robotic surgery team. Despite increased use, publications of comparison studies using the robot-assisted approach are still sparse.

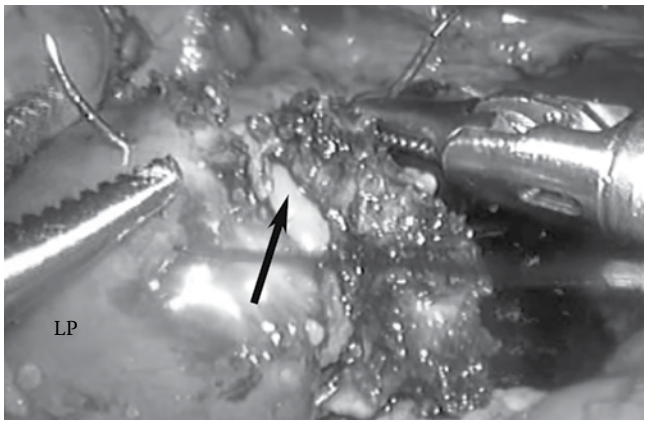

FIGURE 41.6 Closure of the defect after upper-pole removal in a robotically assisted partial nephrectomy. Mattress sutures of monofilament absorbable suture are placed to close the defect. The arrow indicates a pad of retroperitoneal fat that has been placed into the defect to facilitate hemostasis and prevent urinoma formation. LP, lower pole.

Innovative new technologies integrated within the DaVinci system may permit even greater accuracy and safety in certain procedures, particularly partial nephrectomy. Arterial patterns may be mapped out with use of IV indocyanine green, which shows the arterial phase under infrared light.[31]

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CHAPTER 42

Vesicoureteral Reflux: Etiology—Anatomical and Functional

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Vesicoureteral reflux (VUR), a retrograde flow of bladder urine into the upper urinary tract, is one of the most commonly encountered pediatric urological anomalies. It occurs normally in some animal species but is generally considered abnormal in humans. Traditionally, VUR has been categorized etiologically into *primary* and *secondary*. *Primary VUR* is thought to represent an abnormal anatomy and function of the ureterovesical junction (UVJ), whereas *secondary VUR* implies an acquired condition as a result of increased intravesical pressure in the setting of neurogenic bladder dysfunction, nonneurogenic bladder dysfunction, or outlet obstruction. The clinical association of VUR and urinary tract infection (UTI) that leads to pyelonephritis, renal scarring, hypertension, and chronic renal insufficiency (*reflux nephropathy*) has been the primary impetus for diagnostic and therapeutic interventions for VUR. However, various clinical and experimental studies seeking to establish a causal relationship between the pathophysiologic components of VUR, UTI, and other clinical sequelae have led to many contentious debates rather than a unifying consensus. In fact, most pediatric urologists and nephrologists now consider VUR not as a disease in and of itself, but rather as a marker of a heterogeneous condition of the whole urinary tract. It includes congenital renal hypoplasia and dysplasia (in addition to acquired pyelonephritic renal damage), primary reflux caused by incompetent UVJ, altered lower UTI, and inherent predisposition to UTI. In this chapter, the etiological components of VUR—both anatomic and functional—are discussed to establish the conceptual framework within which clinical management issues are presented in the subsequent chapters.

HISTORICAL PERSPECTIVE

Galen and Leonardo da Vinci were the first to propose that a normal UVJ allowed unidirectional flow of urine into the bladder, and that VUR might be abnormal in humans.[1,2] In 1893, Pozzi reported that VUR could occur in humans after noting an unexpected urine leakage from the distal end of an accidentally severed ureter during a pelvic gynecological procedure.[3] Initially, VUR was not thought to be a significant clinical problem for humans. However, in 1903 Sampson began looking closely at the anatomy of the ureter and the pathology associated with ureteral reimplantation after gynecologic procedures. He noted an oblique ureteral entry into the bladder that, upon filling, caused a locking mechanism of the orifice, effectively occluding the lumen from reflux and protecting the kidney from ascending infection.[4] The anatomic relationship was further elucidated in 1929 when Gruber published his work demonstrating that the incidence of reflux varied in relation to the length of the intramural ureter and the muscularity of the detrusor backing.[5]

The systematic identification of VUR came as the result of technological advances in contrast radiography, namely, voiding cystourethrography (VCUG). Consequently, in 1924 Bumpus speculated that VUR was related to UTI and that in children, unlike adults, VUR was not associated with other urinary tract pathology.[6] In 1930, Campbell found VUR in 12% of more than 700 VCUGs but assumed that there was other underlying pathology as the cause of VUR.[7] In 1944, Prather proposed that VUR was abnormal in children,[8] and this notion gained increasing acceptance, after accumulating evidence suggested that VUR was typically absent in normal neonates and children.

The modern era of clinical VUR management was ushered in by Hutch's observation that VUR and pyelonephritis might be causally related in paraplegic patients.[9] Hodson, applying Hutch's concept to children, noted that VUR was more common in children with UTI and renal parenchymal abnormality.[10,11] Expounding upon that relationship, Ransley and Risdon demonstrated the relationship between pyelonephritic scarring, reflux, and infection, effectively defining the pathophysiology of reflux nephropathy.[12] In the era of the VCUG and the accepted pathophysiology of reflux, the grading system for reflux was published by the International Reflux Study Group in 1985.[13] Other clinical and experimental observations soon followed, providing additional anatomical and functional bases for the UVJ mechanism and the etiology of VUR.

DEMOGRAPHIC FEATURES OF VESICOURETERAL REFLUX

In most cases, VUR is discovered clinically after investigation of either UTI or antenatal hydronephrosis. In children without UTI or any other urological problems, the true incidence of VUR is difficult to ascertain but may be

in the order of 0.4%–1.8% of the overall pediatric population.[14,15] In contrast, the incidence of VUR in children with UTI is typically around 30%–50%, with an even higher incidence in infants with UTI.[16–18] Of the 1 of every 500–1200 live births detected to have antenatal hydronephrosis, VUR is identified in about 15%–38% of those infants, with the highest incidence noted in infants with persistent postnatal renal abnormalities.[19,20] Infants with VUR diagnosed from antenatal hydronephrosis show a male preponderance,[21] in contrast to older children who are diagnosed with VUR after presenting with UTI, in which females predominate. Boys tend to present at a younger age, and often have more severe degrees of VUR, especially if diagnosed in infancy.[22] Additionally, urodynamic studies of infants with VUR suggested that high voiding pressures and small functional capacity are more common in boys,[23] which may be explained by a transient urethral obstruction causing high intravesical pressures.

VUR appears to be a heritable disorder, as identical twins have been observed to have a higher incidence of VUR, nearing 80%–100% concordance.[24] VUR occurs in other siblings of affected children as well and is seen at a significantly higher rate than that in the general population (as high as 40%–50%).[25–27] Various studies suggest a dominant inheritance pattern with a variable penetrance. These include an approximate 50% incidence of sibling VUR in the first 2 years of life and a high incidence (about 60%) of parent-to-child transmission.[28] Evidence of genetic heterogeneity has also been published, suggesting that different genes act on different families.[29] These findings bring to light interesting discussions regarding the utility of screening siblings or children of the index patient given the potential increased renal morbidity.

Furthermore, the incidence of VUR varies among races. Children of African ancestry have a lower rate of VUR than those of Caucasian genetic background (ratio of 3.4 to 1),[30,31] and girls of Asian ancestry are suggested to be less likely to have scarring associated with reflux than Caucasian girls.[32] Additionally, studies suggest that the reflux in female children of African descent also resolves at a faster rate[33] and presents with a lower grade.[34] After the age of 10, these rates of reflux seem to equilibrate, suggesting a potential for a delay in antireflux mechanism maturation in Caucasian patients.[35]

ANATOMICAL FEATURES AND EMBRYOLOGIC ORIGINS OF THE URETEROVESICAL JUNCTION

The UVJ is anatomically and functionally adapted to allow intermittent passage of the urinary bolus from the ureter into the bladder while preventing the retrograde flow of bladder urine back toward the kidney during storage and micturition. To achieve these functions, the ureter enters the bladder wall with an oblique intramural path (*intramural ureter*) and extends through a submucosal tunnel of appropriate length (*submucosal ureter*) to open onto the trigone in a correct location. This "flap valve" configuration causes the intramural and submucosal ureter to be compressed with progressive bladder filling against the detrusor muscle backing, as if one were stepping on a compressible straw on the ground (Figure 42.1). This passive action is coupled with an active ureteral–trigonal mechanism, resulting in maintenance of an intact UVJ and the prevention of reflux.

The active component of the UVJ mechanism requires a functional integration of the ureter with the bladder and trigone. Functional components of the UVJ were first appreciated when Bell, in 1812, noted that extension of the ureteral longitudinal muscle fibers into the trigone (*Bell's muscle*) was important in the preservation of intramural ureter obliquity.[37] An anatomic description of these intravesical fibers was then further elucidated by Tanagho and Pugh,[38] demonstrating that the inner longitudinal ureteral fibers formed the superficial trigone, down to the level of verumontanum in males and the dorsal surface of the

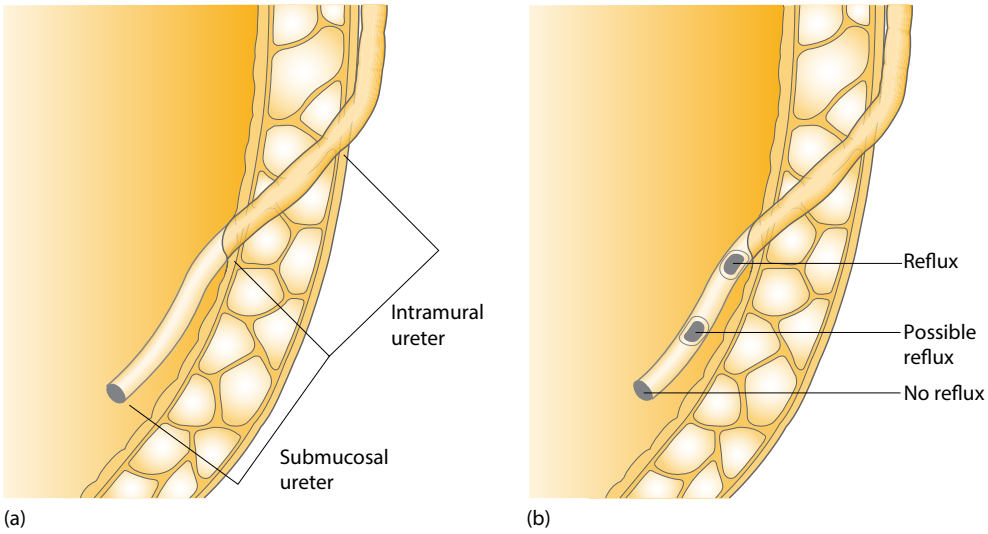

FIGURE 42.1 (a) Normal UVJ: Demonstration of the intravesical ureter (intramural + submucosal). (b) Refluxing UVJ: In contrast to nonrefluxing orifice, there is an inadequate length of the intravesical ureter, compromising the flap valve mechanism. (From Politano VA. Vesicoureteral reflux. In Glenn JF, ed., *Urologic Surgery*, 2nd edn. New York: Harper & Row, 1975, 272–93.)

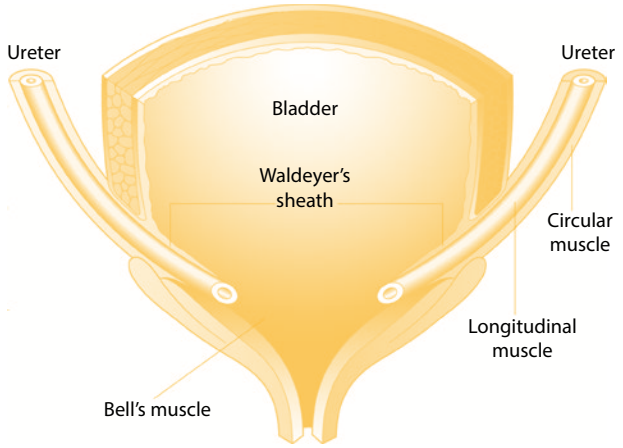

FIGURE 42.2 Passage of the distal ureter through the ureteral hiatus in the bladder wall. Ureteral inner longitudinal muscle fibers extend into the trigone to form Bell's muscle. The Waldeyer sheath anchors the distal ureter at the hiatus. (From Mathisen W. *Surg Gynecol Obstet* 1964;118:965–71.)

urethra in females. Here the muscle fibers extend fanwise and, at the midline of the trigone, intermingle with those of the contralateral ureter. The middle circular ureteral muscle is not seen beyond the level of the ureteral hiatus, and the adventitia of the distal ureter just outside the bladder wall fuses with the fibromuscular sheath that encircles the ureter (known as the *Waldeyer sheath*). The Waldeyer sheath is thought to anchor the ureter within the hiatus while allowing the intramural ureter to slide freely within the hiatus during bladder filling and emptying (Figure 42.2). This is essential to the ureter's ability to efflux, as this mobility allows for the shortening and widening of the ureter in response to a bolus of urine.

In 1972, Elbadawi[40] (and later confirmed by Stephens[41]) identified a separate intermediate layer extending from the ureter into the deep trigone. Immunohistochemical studies also confirmed these intermediate ureteral muscle extensions into the deep trigone and noted that they are richly innervated by noradrenergic receptors, similar to vasa deferentia,[42] and fan out into the trigonal region along with the muscle fibers.[43] Interestingly, this intermediate layer may be important in the overall development of the ureteral trigonal relationship, and embryologically, ureteral maldevelopment may be linked with an abnormal trigonal development. (This thought is supported by a recent study of vitamin A signaling–deficient mice demonstrating an abnormal development of trigone, thereby resulting in a high incidence of distal ureteral anomalies.[44])

Despite somewhat conflicting opinions about the precise anatomical details of the ureter–trigone relationship, there is sound physiologic evidence to suggest that a functional integration of the ureter and trigone is important in the normal UVJ mechanism. From a neuroanatomical standpoint, Tanagho's series of elegant experiments in dogs helped define these roles in preventing VUR[45] and suggested an important neuronal involvement, as a unilateral sympathectomy at L3–5 uniformly induced reflux. These findings were consistent with earlier observations by Langworthy in 1938, where unilateral sympathectomy in cats induced unilateral dilated ureter with ipsilateral widening of the ureteric orifice. Smooth muscle integration has also been found to be necessary in this process, as studies suggest distal ureteral smooth muscle atrophy, dysplasia, and architectural derangement and extracellular matrix remodeling in refluxing ureters.[46,47] Additional experiments demonstrated that increasing the trigonal tone and contractility using electrical stimulation, epinephrine injection, bladder distention, and micturition all resulted in functional occlusion of the ureteric orifices. Furthermore, surgical incision of ureter–trigone continuity below the ureteric orifice resulted in VUR, which then disappeared after healing of the incision.

In addition to the experimental observations noted above, clinical findings lend further support for the importance of the flap valve mechanism in preventing VUR, specifically in relation to the length of the intravesical ureter and the lateral displacement of the ureteric orifice. The intravesical ureter (the intramural segment plus the submucosal tunnel) has been estimated to lengthen with age, providing rationale for spontaneous VUR resolution with maturation. In neonates, the average length of the intravesical ureter was 0.5 cm, while in adults, it was 1.3 cm,[48,49] and the mature length was thought to be achieved by 10–12 years of age. Trigonal competency also plays a critical role in maintaining the adequate length and obliquity of the intravesical ureter during bladder distention and micturition, further supporting the importance of this relationship. Inadequate trigonal function allows the ureteric orifice to displace laterally and migrate away from the bladder neck during bladder filling, leading to reduction of the intravesical ureteral length.

The lateral displacement of the ureteric orifice and its abnormal appearance in association with VUR are well established (Figure 42.3). The classic explanation proposed by Mackie and Stephens suggests that the lateral displacement may occur as the result of abnormal ureteric

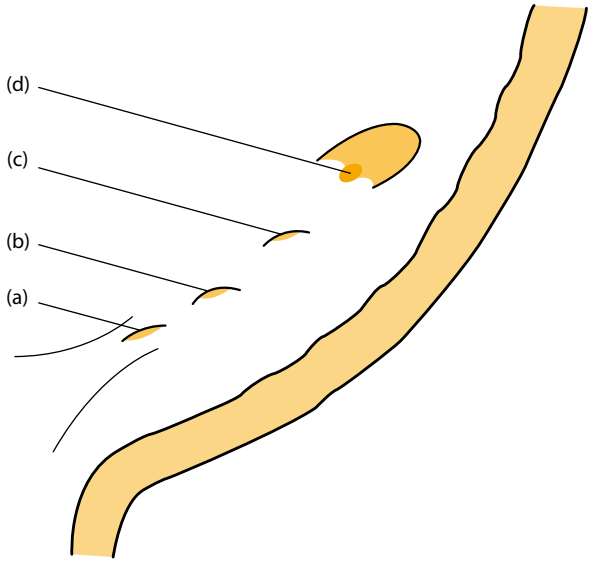

FIGURE 42.3 Four different ureteric orifice positions. (a) Normal. (b) Moderately lateral. (c) Very lateral. (d) Orifice at the mouth of a diverticulum. (From Glassberg KI, Hackett RE, Waterhouse K. Congenital anomalies of the kidney, ureter, and bladder. In Kendall AR, Karafin L, Goldsmith HS, eds., *Urology*. Philadelphia: Harper & Row, 1987, 158.)

bud origin along the developing mesonephric duct.[51] They found a correlation between the lateral displacement of ureteric orifice and the degree of renal dysplasia and hypoplasia. They postulated that the ectopic origin of ureteric bud during the metanephric development was the primary embryological error leading to anomalous renal differentiation and an abnormally located ureteric orifice. This view is most plausible when applied to duplex system anomalies but may also be pertinent to the congenital renal anomalies associated with VUR. An alternative embryological view of the VUR may be the concept of primary trigonal disorder, as previously discussed. The trigone develops as a result of common nephric duct and the distal ureter incorporation into the developing bladder, and it is reasonable to postulate that the lateral displacement and the abnormal ureteral anchoring may occur as a result of functional disorganization of the trigone during development.[44]

Endoscopic observations have helped in confirming the importance of the flap valve mechanism in preventing VUR as well. Specifically, the ratio of the submucosal tunnel length to the ureteral diameter appears to be a critical factor that determines the effectiveness of UVJ function.[48,49] Paquin noted that in children without VUR, the ratio of tunnel length to ureteral diameter was 5 to 1, whereas in children with VUR, the ratio was 1.4 to 1. Cussen documented the relationship between intravesical ureteral length, submucosal ureteral length, and ureteral diameters in normal infants and children (Table 42.1).[49] The relative position and shape of the ureteric orifice also seem to correlate with the length of the intravesical ureter. Orifices that are placed laterally, away from the bladder neck, are associated with a higher incidence of VUR and probably reflect poor trigonal anchoring and short intravesical ureteral length. Lyon and colleagues described four basic orifice shapes that reflect the competency of the UVJ anatomy: cone, stadium, horseshoe, and golf hole.[52] VUR was seen in 4% of patients with a normal cone configuration, in 28% of those with a stadium orifice, in 83% of those with a horseshoe orifice, and in 100% of those with a golf-hole orifice. Heale confirmed Lyon's observations by reporting a higher prevalence and grade of VUR, as well as renal scarring, in patients with more laterally placed and abnormal ureteric orifices.[53] Stephens described another orifice configuration—the lateral pillar defect—which probably represents a type of ureter–trigone abnormality between horseshoe and golf-hole orifices.[54] Although an endoscopic appearance of ureteric orifices is no longer considered a particularly reliable clinical indicator of VUR (especially in low- to moderate-grade

TABLE 42.1 Ureteral tunnel lengths and diameters in children

Age (years)	Intravesical ureteral length (mm)	Submucosal ureteral length (mm)	Ureteral diameter (mm)
1–3	7	3	1.4
3–6	7	3	1.7
6–9	9	4	2.0
9–12	12	6	1.9

Source: Cussen LJ. *Invest Urol* 1967;5:164–78.

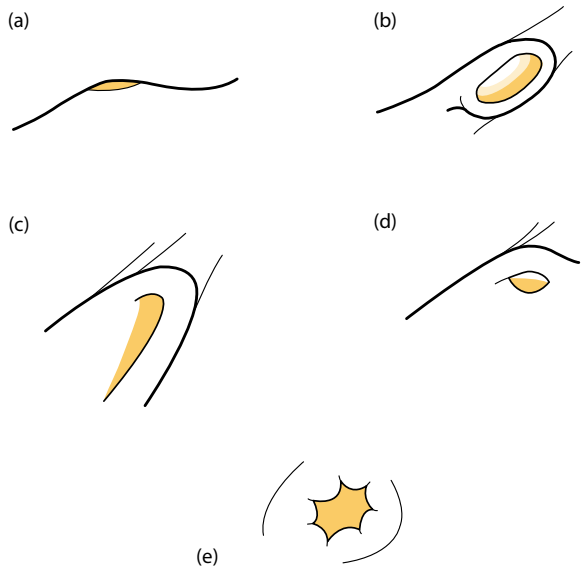

FIGURE 42.4 Orifice morphology (endoscopic view). (a) Normal cone-shaped orifice. (b) Stadium orifice. (c) Horseshoe orifice. (d) Lateral pillar defect. (e) Golf-hole orifice. (From Glassberg KI, Hackett RE, Waterhouse K. Congenital anomalies of the kidney, ureter, and bladder. In Kendall AR, Karafin L, Goldsmith HS, eds., *Urology*. Philadelphia: Harper & Row, 1987, 158.)

situations), these observations provide insight into the overall mechanism of competence of the UVJ (Figure 42.4).

The anatomical mechanisms of the UVJ combining active and passive mechanisms can be summarized as follows. The natural tone of ureteral muscle provides a mild passive closure of the intramural ureter except during the efflux of the urinary bolus. As the bladder fills and becomes distended, there is a progressive obliquity of the intramural and submucosal ureter, creating a "flap valve" mechanism, provided that there is a sturdy back wall support of the detrusor muscle. The tone and contractility of the trigone increase steadily during bladder filling as it becomes stretched, and it provides a secure anchoring of the ureteric orifices, further augmenting the flap valve mechanism. Micturition also stimulates the trigonal tone via a complex integration of muscle and neuronal mechanisms, anchoring the ureter and preventing the lateral displacement of the orifice. The critical factor of this flap valve mechanism is the effective occlusion of the intramural and submucosal ureter as the rising intravesical pressure compresses it against the detrusor muscle. The anatomical and functional integration of the ureter and trigone is a remarkable piece of bioengineering, which allows an unimpeded unidirectional flow of urine at the UVJ.

PRIMARY VERSUS SECONDARY VESICOURETERAL REFLUX AND THE ROLE OF LOWER URINARY TRACT FUNCTION

The distinction between *primary* and *secondary* VUR is important in the conceptualization of contributing

pathophysiology and relevant anatomic and functional etiologies that need to be addressed clinically. In certain cases, the distinction is not entirely clear in that some forms of primary VUR may be associated with bladder anomalies, which contribute to the progression of the underlying UVJ malfunction. The clinical reality is that in all patients presenting with VUR, the proper management must include a global view of the entire urinary tract, including UVJ mechanism, bladder dysfunction, predisposition to UTIs, and renal anomalies. A short intravesical ureter or a marginally competent ureter–trigone complex may increase the likelihood of VUR in unfavorable conditions, such as bladder hypertonicity, high-pressure voiding, and UTI. On the other hand, an extremely competent UVJ may resist VUR even in cases of challenges by an abnormal bladder until there is an irreversible deformation of the UVJ structures.

The concept of secondary VUR is critical in that understanding the dynamic process of reflux would be incomplete without considering the effect of the bladder. In a normal, mature urinary tract, increasing the intravesical pressure alone does not necessarily induce VUR. However, VUR can be acquired secondary to bladder anomalies, such as neurogenic bladder disorders and various types of bladder outlet obstruction (as in boys with posterior urethral valves). The chronic elevation of bladder pressure and the subsequent distortion of the bladder wall at the UVJ (such as paraureteral diverticulum) may be critical in the formation of secondary VUR as the pressure elevation overwhelms the flap valve mechanism. The structural and neurological perturbation of the trigone in the abnormal bladder is likely to be important as well.

The most common anatomic cause of secondary VUR is seen in boys with posterior urethral valves, which are associated with VUR in more than 50% of patients.[55] Reflux may resolve in 30%–70% of these patients at 6 months with valve ablation and relief of the high-pressure voiding.[56] Anatomic obstructions causing VUR in girls are rare and may occur in the setting of an obstructing ureterocele. Again, this VUR often resolves after decompression of the ureterocele.

Overall, any child with an altered bladder function is at risk for secondary VUR. A poorly compliant bladder, along with its abnormal interaction with dyssynergic urinary sphincters, can lead to increased intravesical pressures, which then weaken and alter the UVJ to cause VUR. McGuire et al. demonstrated that if the bladder pressures exceeded 40 cm H_2O, the incidence of VUR was seen in more than 80% of patients with myelodysplasia and neurogenic bladders.[57,58]

In infants and children, abnormal lower urinary tract function often coexists with VUR without any apparent neurogenic or anatomic pathology. These observations further suggest a role of lower urinary tract function in the pathogenesis of VUR and its implication in the clinical management of the condition. To start, elevated voiding pressures, especially in infants, may play a central role in VUR pathophysiology. Infantile bladders have been shown to have high voiding pressures. Urodynamic studies have shown that this may be the result of imperfect coordination between detrusor contraction and sphincter relaxation.[59,60] This pattern of immaturity typically disappears after 2 years, and is thought to result from a lack of integration between the bladder, the external urethral sphincter, the brainstem, and the higher cortical centers. Compared with normal infants, those with VUR have an even higher voiding pressure and abnormal bladder function, even in the absence of UTI.[59] A discoordinated pattern of voiding was the most common urodynamic abnormality in both male and female infants with VUR. Additionally, abnormally high voiding pressures with small functional bladder capacity or poor bladder contractility with inadequate emptying was seen primarily in boys. Others have also noted an increased incidence of bladder "hypercontractility" in infant boys with VUR.[61] This higher voiding pressure and its association with a higher incidence of high-grade VUR in infant males has been attributed to transient urethral obstruction, especially when intravesical ureteral tunnels are not fully mature.

In a fetal sheep model of VUR, defunctionalization of UVJ (surgical unroofing of the submucosal ureter) was insufficient to produce VUR reliably in females, who also required a partial ligation of the urethra in order to reproduce a similar degree of VUR as seen in males with UVJ unroofing only.[62] Such experimental observations, along with VUR-associated urodynamic abnormality analogous to that seen in boys with posterior urethral valves, led to a speculation that transient urethral obstruction may be the cause of infantile VUR in some cases.

The abnormal urodynamics seen in infants with VUR may also imply a global maldevelopment of the trigone and proximal urethral mechanism, which needs to funnel open in coordination with detrusor contraction in order to induce efficient, low-pressure emptying. Godley and colleagues studied the clinical outcome of infants with VUR in relation to the overall renal status and the bladder function and found that those with abnormal kidneys were more likely to have an abnormal bladder function, as well as failure of VUR resolution.[63] These observations further support the notion that the entire spectrum of VUR disorder—reflux, renal anomaly, and bladder dysfunction—may result from the primary maldevelopment of the ureter–trigonal complex.[44,51]

Symptoms of pediatric voiding dysfunction—frequency, urgency, and enuresis—lie on a spectrum with detrusor instability (DI) and/or detrusor sphincter dyssynergia (DSD), and they are often found in patients with UTI and VUR. In a study of more than 360 children with dysfunctional voiding, 60% had UTI and 20% had VUR.[64] The European branch of the International Reflux Study found the presence of dysfunctional voiding in 18% of more than 300 children with VUR and UTI,[65] and urodynamic investigation showed that DI may be found in up to 60% of children with VUR.[66,67] Despite these well-documented associations, it is unlikely that VUR is directly caused by DI in most cases. Many more children have DI than VUR. There are also reports showing no statistical causal association between DI and VUR.[68] However, in patients with marginally competent UVJ, DI may exaggerate the VUR. It is generally accepted that unrecognized DI can delay the resolution of VUR, and there are reports that the treatment of DI with anticholinergics can facilitate the VUR resolution.[66,69] Some studies, however, have

not shown any beneficial effect of anticholinergic therapy in the elimination of VUR.[70]

Although DI may not induce VUR directly, it plays an important role in the overall pathophysiology of the VUR–UTI–nephropathy complex. The presence and severity of dysfunctional voiding symptoms correlated significantly with the persistence of VUR during medical management and further correlated with the UTI recurrence regardless of surgical correction of VUR.[65] In fact, the mutual association of DI and VUR to UTI may explain its clinical coexistence in many clinical scenarios.

ROLE OF UTI IN VESICOURETERAL REFLUX

Tanagho and colleagues proposed that lower urinary tract inflammation might affect the mildly deficient UVJ and induce VUR.[45] New VUR was reportedly acquired in six out of seven experimental piglets after *Escherichia coli* infection and bladder inflammation.[71] Some *E. coli* strains have been implicated to affect the activity of urinary tract smooth muscle directly, rather than via inflammatory reaction. Bacterial endotoxin was found to inhibit α-adrenergic receptors of trigonal musculature in cats.[72] Similarly, UTI may cause human ureteral dilatation.[73,74] Such a direct effect of bacterial infection on ureteral smooth muscle function could conceivably induce ureter–trigonal dysfunction, thereby facilitating VUR. Since UTI is also known to induce bladder hypercontractility and lower the compliance, a combined challenge of both ureter and bladder muscle dysfunction by UTI may well cause VUR in patients with marginally competent UVJ.

Clinically, it had been suggested that VCUG performed at the time of ongoing UTI might "falsely" demonstrate VUR, which was not present when the urine was sterile. Gross and Lebowitz surveyed more than 600 children undergoing cystographic evaluation for VUR and found no evidence of increased VUR in the setting of positive urine cultures.[75] In other words, their data did not support the notion that VUR was caused by UTI.

Whether the combined challenge of UTI and abnormal bladder dynamics leads to the *secondary* (or acquired) VUR or merely discloses preexistent *primary* VUR, it is clear that they are critical cofactors to contend with in the overall management of patients with VUR.

CONCLUDING REMARKS

Although VUR remains a significant and commonly encountered clinical problem in pediatric urology, VUR may be a normal transitory phenomenon in many species and in some humans. It is a dynamic process involving anatomical and functional anomalies and maldevelopment of the ureter–trigone complex and the UVJ, as well as the effects of UTI and lower urinary tract dysfunction. The clinical significance of VUR must be interpreted in the context of global urinary tract anomalies, including bladder dysfunction, inherent predisposition to UTI, and congenital or acquired reflux nephropathy.

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CHAPTER 43

Nonsurgical Management of Vesicoureteral Reflux

Jack S. Elder and Mireya Diaz

INTRODUCTION

In a child with vesicoureteral reflux (VUR), the primary goal of therapy is to prevent pyelonephritis, because repeated upper urinary tract infection (UTI) can lead to renal scarring and, in some cases, hypertension, reduced somatic growth, renal insufficiency, and end-stage renal disease (ESRD). In addition, reflux-related complications during pregnancy may occur. If a child with VUR already has reduced renal function, then additional treatment may be necessary to preserve existing renal function as the child grows. The clinical factors that place the patient at risk for these complications include high VUR grade, female gender, presence of bladder–bowel dysfunction (BBD), and presence of renal scarring.

Nonsurgical therapy is based on the following principles: (1) higher grades of VUR increase the risk of developing pyelonephritis; (2) VUR often resolves over time; (3) sterile VUR is not harmful to the kidneys, if bladder function is normal; (4) UTI in the presence of VUR can result in acute pyelonephritis, which can result in renal scarring; and (5) the morbidity or complications of VUR can be decreased by preventing UTI. In contrast, the principle of surgical therapy is that the risks associated with VUR and nonsurgical therapy can be minimized or prevented with surgical correction. The benefits and risks of these two approaches must be considered when deciding on a course of therapy.

Options for nonsurgical therapy include

1. Antibiotic prophylaxis
   a. Daily
   b. Intermittent (i.e., treatment of UTIs when they are diagnosed)
2. Bladder training (urotherapy)
3. Treatment of BBD: Timed voiding
   a. Treatment of constipation
   b. Anticholinergic
   c. Alpha-blocker
   d. Biofeedback
4. Periodic assessment of reflux and child well-being
   a. Serial assessment of blood pressure, renal function, and somatic growth
   b. Serial urinalysis or urine culture
   c. Serial voiding cystourethrogram or radionuclide cystogram
   d. Serial upper urinary tract studies

An individualized approach to each child utilizing shared decision making with parents takes into account the child's gender, VUR grade, age, presentation (UTI, sibling screening, and antenatal diagnosis), renal status at the beginning of therapy, compliance with treatment, likelihood of reflux resolution, and parent and child preferences.

REFLUX RESOLUTION

The decision to choose nonsurgical management in a child with VUR is based on the fact that reflux often resolves, and when it resolves, the risk of upper tract infection is reduced. The exact mechanism of reflux resolution is unknown. Presumably, the intramural ureteral tunnel lengthens with bladder growth and with bladder functional maturation.

VUR resolution is most likely in younger children and those with lower reflux grades (Figure 43.1). The 1997 American Urological Association (AUA) Pediatric Vesicoureteral Reflux Practice Guidelines Committee analyzed the raw data from several series in which long-term treatment was nonsurgical to develop these figures.[1–4] At 5 years, approximately 92% with grade I and 81% with grade II VUR showed resolution, irrespective of age at presentation or whether the reflux was unilateral or bilateral. On the other hand, in grade III VUR, resolution was highest for unilateral grade III reflux in children less than 2 years (70%) and lowest for children with bilateral grade III reflux over 5 years at diagnosis (12.5%). In contrast, in a large series by Greenfield et al., for children with grade III VUR, resolution was similar irrespective of age at presentation.[5] In the AUA series, unilateral grade IV VUR resolved in 50% at 5 years, whereas only 10% of those with bilateral grade IV VUR resolved.[1] For grade IV VUR, age was not stratified because of small patient numbers. In a report of 80 infants who were <6 months at diagnosis with grades III–V VUR, resolution of VUR (including reduction of VUR grade to I or II) occurred in 62%.[6] These children

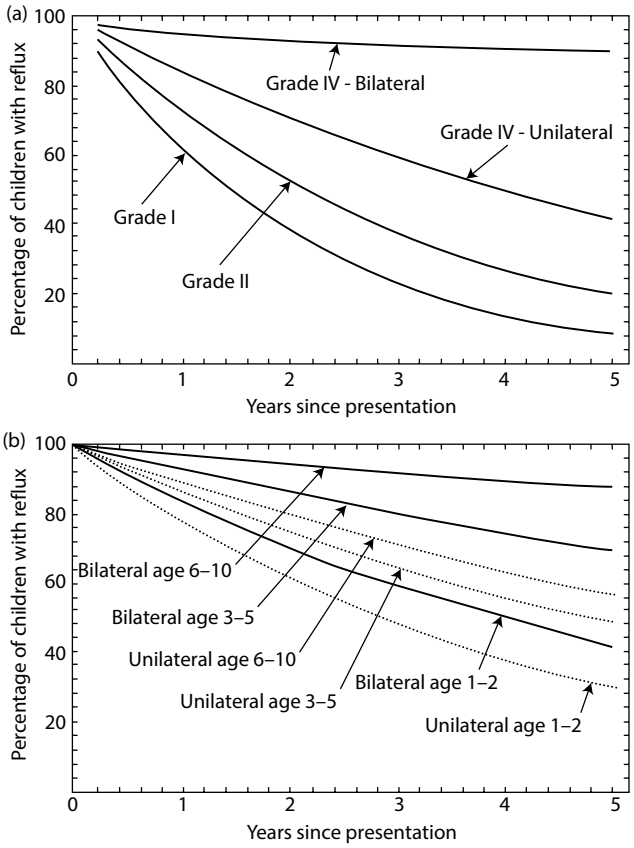

FIGURE 43.1 Percent chance of reflux persistence for 1–5 years following presentation. (a) Grades I, II, and IV reflux (bilateral and unilateral). (b) Grade III reflux by patient age reflux laterality at presentation. (Reprinted from Elder JS et al. *J Urol* 1997;157:1846–51.)

were diagnosed following either an antenatal diagnosis of hydronephrosis or a UTI. Overall, only 25% had surgical correction. A normal initial dimercaptosuccinic acid (DMSA) scan, an initial reflux grade of less than V, and the absence of breakthrough febrile UTIs were predictive of reflux resolution or improvement. There are more recent nomograms for predicting VUR resolution rates,[7] but they include a large number of children that drop out for surgery. This diminishes the number of medically treated children with VUR and might bias the reported resolution rate.

There is little available observational follow-up that is longer than 5 years. Ten-year follow-up of the medical treatment arm of the International Reflux Study showed reflux resolution in 73% of those with unilateral grade III or IV VUR.[8] In children with grade III or IV VUR on one side and grade I or II on the other, 49% had resolved, and in those who presented with bilateral grade III or IV VUR, only 39% resolved. In a series from Children's Hospital of Philadelphia, 10/51 children (19.6%) (mean age 8.6 years) who were taken off antibiotic prophylaxis demonstrated VUR resolution, and 5/51 (9.8%) developed a febrile UTI.[8] It is known that VUR can resolve during adolescence. For example, in the series by Lenaghan, VUR resolution was reported in 20%, but their patients were not studied systematically.[9]

The timing of VUR during a voiding cystourethrogram can predict reflux resolution. If VUR occurs during bladder filling, when bladder pressure is low, it is much less likely to resolve or improve significantly, whereas if VUR is demonstrated only during voiding, when bladder pressure is high, it is much more likely to resolve over time.[10,11] Bladder capacity does not appear to be a relevant factor. Bael et al. demonstrated that bladder capacity varies widely in children with VUR, and that there is no relationship between bladder capacity and reflux grade or likelihood of VUR resolution.[12]

ANTIBIOTIC PROPHYLAXIS

In the past, the cornerstone of UTI prevention was daily antimicrobial prophylaxis. The basis for prophylaxis is that in the 1960s and 1970s, children with VUR were managed by treating each UTI as it occurred, i.e., intermittent therapy. Several retrospective studies of children with VUR suggested that the rate of new renal scar formation was significantly lower in children receiving prophylaxis (as low as 3%).[3,5,13,14] In addition, it was concluded that girls with VUR were more likely to develop renal scars than boys, renal scars can occur at any age, children with mild VUR were at risk for scar formation, and scarring could occur in normal kidneys. Several earlier studies suggested that new renal scarring occurred primarily in children with a breakthrough febrile UTI.[2–5] However, there is also evidence that new scarring can occur in older as well as young children.[15–18] The efficacy of prophylaxis in preventing the ultimate complication of renal scarring, ESRD, was questioned in a review of the Australia and New Zealand Dialysis and Transplant Registry from 1971 to 1998, in which no significant reduction of ESRD secondary to VUR was observed, despite implementation of routine prophylaxis for VUR.[19]

More recently, there has been considerable concern regarding the risk of bacterial resistance resulting from inappropriate use of antibiotics, and many parents question the benefit and safety of continuous antibiotic prophylaxis (CAP). Furthermore, several prospective randomized clinical trials have demonstrated that prophylaxis in children with VUR is often ineffective. These series are summarized in Tables 43.1 and 43.2.[20–27] Four of the seven prospective trials suggested that there was no benefit to prophylaxis in children with VUR. As is common in clinical trials, there was significant variation in the quality of these studies, and most of the children had low-grade VUR. However, the Swedish Reflux Trial, which studied children ages 1–2 years with grades III and IV VUR, demonstrated a clear advantage to prophylaxis in girls.[25] In this study, no child receiving prophylaxis developed a new renal scar.[26] The benefit of prophylaxis in this study of dilating VUR was statistically significant in girls, but not in boys. The study by Craig et al. indicated that the rate of UTI was diminished from 19% (placebo) to 13% (prophylaxis).[24] The most recent trial was RIVUR (Randomized Intervention for Vesicoureteral Reflux). This trial was a randomized prospective double-blind placebo-controlled study of 607 children, ages 2–72 months (median 12 months), 92% of whom were girls.[27] After 2

TABLE 43.1 Randomized trials of antimicrobial prophylaxis for vesicoureteral reflux

Authors	Randomized/ placebo controlled	Patient age	Number studied	Patients included	No. With vur	Vur grade	Urine collection in non-toilet-trained children	Definition of uti	Duration of follow-up (months)
Garin et al.[20]	Yes/no	1 month–18 years	218	UTI ± VUR	113	I–III	Bladder catheterization if unable to void	Pyuria + significant bacteriuria	12
Roussey-Kesler et al.[23]	Yes/no	1 month–3 years	225	UTI + VUR	225	I–III	Bags	Significant bacteriuria	18
Pennesi et al.[21]	Yes/no	0 month–2½ years	100	UTI + VUR	100	II–IV	Clean catch, bladder catheterization in septic patients	Pyuria + significant bacteriuria	24–48
Montini et al.[22]	Yes/no	2 months–7 years	338	UTI ± VUR	128	I–III	Bag	Pyuria + significant bacteriuria	12
Craig et al.[24]	Yes/yes	0–18 years	576	UTI ± VUR	243	I–V	Clean catch, bladder catheterization, or suprapubic aspiration	Significant bacteriuria	12
Brandström et al.[25]	Yes/no	1–2 years	203	VUR	137[a]	III–IV	Clean catch, bag, or suprapubic aspiration	Significant bacteriuria	24
RIVUR Trial Investigators[27]	Yes/yes	2–71 months	607	UTI + VUR	607	I–IV	Catheterization or suprapubic aspiration	Pyuria, significant bacteriuria, fever, or UTI sx	24

Abbreviation: sx, symptoms.
[a] Endoscopic treatment arm excluded.

TABLE 43.2 Results of randomized trials of antimicrobial prophylaxis for vesicoureteral reflux

	Recurrent uti				Renal scarring				
		Rate of recurrent uti					Renal scarring on dmsa		
Authors	No. of patients with vur	With prophylaxis	Without prophylaxis	Relative risk	No. With dmsa renal scan	Patients included	With prophylaxis	Without prophylaxis	Relative risk
Garin et al.[20]	113	13/55 (24%)	13/58 (22%)	1.05	113	UTI + VUR	5/55 (9.0%)	2/58 (3.4%)	2.6
Roussey-Kesler et al.[23]	225	18/103 (17%)	32/122 (26%)	0.66	N/A		N/A	N/A	N/A
Pennesi et al.[21]	100	18/50 (36%)	15/50 (30%)	1.20	100	UTI + VUR	22/50 (44%)	18/50 (36%)	1.22
Montini et al.[22]	128	10/82 (11%)	21/121 (17%)	0.62	295	UTI ± VUR	50/187 (26.8%)	33/108 (30.5%)	0.87
Craig et al.[24]	243	14/122 (11%)	21/121 (17%)	0.66	154	UTI ± VUR	35/71 (49%)	38/83 (46%)	1.07
Brandström et al.[25,26]	137	10/69 (15%)[a]	25/68 (37%)[a]	0.39	136	VUR	4/68 (6%)	12/68 (18%)	0.33
RIVUR Trial Investigators[27]	607	39/302 (13%)	72/305 (24%)	0.55	447	UTI + VUR	18/220 (8%)	19/227 (8%)	0.98

Abbreviation: N/A, not available.
[a] Febrile UTI.

years, trimethoprim-sulfamethoxazole (TMP-SMZ) prophylaxis diminished the risk of UTI by 50%. The benefit was most apparent in children who had had a febrile UTI before entry and in those with BBD. However, the rate of new renal scarring was similar in the two treatment groups (11.9% vs. 10.2%).

A unique aspect of the RIVUR study is that TMP-SMZ resistance of *Escherichia coli* isolates was evaluated by rectal swab at study entry, at 24 months, and following an occurrence of treatment failure.[27] Overall, the authors found an insignificant difference in *E. coli* resistance between the prophylaxis group (27.6%) and the placebo group (19.5%). However, in the children who experienced treatment failure secondary to *E. coli*, 19/30 (63.3%) receiving TMP-SMZ prophylaxis had resistant stool isolates, compared with 11/57 (19.3%). With regard to antibiotic adherence (i.e., compliance), 77% of the families reported having administered the prescribed medication at least 75% of the time. Of the children receiving the prophylactic TMP-SMZ, 91/302 (30%) of the parents reported having discontinued administration of the drug. In a "real-world" study from a national pharmacy claims database, antibiotic adherence was only 40%.[28]

The 2010 AUA VUR guidelines recommended prophylaxis for children less than 1 year of age, whereas in children over 1 year, it was a treatment option.[29] In addition, if a child with VUR not receiving prophylaxis developed a febrile UTI, it was recommended that initiation of prophylaxis should be considered. These guidelines were based on studies reported through 2008 and did not include the Swedish Reflux Trial, which was reported in 2010 and strongly supported prophylaxis in girls with grades III and IV VUR; the Craig trial; or the RIVUR trial.

Consequently, daily antibiotic prophylaxis appears to be beneficial in girls with grades III–V VUR and boys with grades IV and V VUR. On the other hand, children with grades I and II VUR and boys with grade III VUR may not benefit from prophylaxis, unless they have BBD (see below).

Common medications used for prophylaxis include TMP-SMZ, nitrofurantoin, TMP, and cephalexin. Generally, a dosage that is one-quarter to one-half of the full dose is prescribed, and administration at bedtime theoretically yields the optimal benefit. Although it has been assumed that TMP and SMZ are synergistic in the treatment of UTI, it has been demonstrated that TMP alone is as effective as the combination medication, and significantly more effective than SMZ in the treatment of *E. coli* UTI.[30] Edlin et al. demonstrated that in an outpatient setting, *E. coli* resistance to nitrofurantoin was only 1%, vs. 24% for TMP-SMZ.[31] Nitrofurantoin and TMP are excreted only in the urine and do not induce a change in bowel flora.

Antibiotic resistance is receiving significant exposure in the press, and recently, the World Health Organization released an extensive report on its efforts for global surveillance on antibiotic resistance.[32] In this era of shared decision making, parents will be increasingly uncomfortable administering a daily antibiotic or antimicrobial unless there is good evidence for its benefit for their child. In addition, in the case of VUR, parents may choose surveillance or surgical therapy (endoscopic, open, or minimally invasive) over prophylaxis.

Potential adverse effects of nitrofurantoin suspension include gastric upset, nausea, and a very poor taste to the medication. Use of nitrofurantoin macrocrystals in a capsule can obviate these problems. In young children, the capsule may be opened and the macrocrystals can be mixed with food or formula. More serious side effects are rare, with one study documenting only 40 reports out of 8.6 million uses.[33] TMP-SMZ is generally well tolerated, although Uhari et al. reported that the medication was changed because of adverse effects in 15% of children receiving sulfonamides and 8% receiving TMP.[34] The most common adverse effect is allergic skin reaction, usually from the sulfa component. This problem may occur following several weeks or months of therapy, but anaphylaxis is rare. Although neutropenia, thrombocytopenia, and/or eosinophilia occurs in 12%–34% of children receiving full-dose TMP-SMZ for only 10 days,[35] the incidence of these side effects in children receiving prophylactic dosages as long as 1 year is quite low.[36] Photosensitivity is another concern with sulfa-based antimicrobials. An additional potential complication is dental caries secondary to the fructose in the liquid preparation, but this problem can be prevented by having the children brush their teeth after taking the drug. The most serious potential side effect is Stevens–Johnson syndrome, but this reaction is extremely rare.

In babies up to 2 months of age, amoxicillin or cephalexin should be prescribed instead of a sulfa-based antibiotic or nitrofurantoin. Typically, 50–75 mg once or twice daily (either amoxicillin or cephalexin) is prescribed.

BLADDER–BOWEL DYSFUNCTION

BBD is one of the most important clinical factors contributing to recurrent febrile UTI and renal scarring in children with VUR.[29,37] BBD is used to describe children with abnormal lower urinary tract symptoms of storage and/or emptying, which include lower urinary tract conditions, such as overactive bladder and urge incontinence, voiding postponement, underactive bladder, and dysfunctional voiding, and may also include abnormal bowel patterns, such as constipation and encopresis.[29] Many of the terms pertaining to abnormal lower urinary tract symptoms were described in an article on nomenclature published by the International Children's Continence Society (ICCS).[38]

The effect of bladder dysfunction on VUR has been recognized for many years. In 1979, Koff et al. studied 53 neurologically normal children with UTI and detrusor sphincter discoordination and found that 50% had VUR.[39] In 1983, Koff and Murtagh reported that in children with VUR, uninhibited bladder contractions, and voluntary sphincter contraction, treatment with anticholinergics resulted in a threefold increase in VUR resolution and fourfold reduction in UTI.[40] In 1985, Noe retrospectively studied 305 patients undergoing ureteral reimplantation for primary reflux and noted that reflux persisted postoperatively in 11, of whom 6 required a secondary procedure. All 11 children had diurnal and nocturnal enuresis, frequency, urgency, and squatting, while 4 had

straining and an interrupted urinary stream, 2 had significant postvoid residual urine, and 3 had a neurogenic configuration of the bladder on cystography.[41] In 1991, Snodgrass reviewed 109 children with UTIs or dysfunctional voiding without UTI and found that one-third of girls with VUR had dysfunctional voiding, and 21% of girls with dysfunctional voiding had VUR, suggesting an association between these two conditions, but not a cause-and-effect relationship.[42]

In 1998, in a landmark retrospective study, Koff et al. reported that bowel disorders also contribute to VUR morbidity, and coined the term *dysfunctional elimination syndrome* (DES).[43] In a retrospective study of 143 children with primary VUR, DES was present in 43% of children thought to have primary VUR. Of these, 82% had breakthrough UTIs and underwent ureteral reimplantation, compared with 18% with VUR without DES. Following the disappearance of VUR, UTI developed in 18 children, including 14 (78%) with DES. Unsuccessful surgical outcomes involving persistent, recurrent, and contralateral VUR occurred only in children with DES. Unfortunately, this study was published the year after the initial AUA VUR guidelines, and its importance was not recognized until the second AUA VUR guidelines report.

Snodgrass reported a series of 128 children with VUR, 66 of whom had dysfunctional voiding and underwent treatment with anticholinergic therapy and antibiotic prophylaxis.[44] Although the VUR resolution rate was similar among those with and without dysfunctional voiding, 43% of those with BBD had a breakthrough UTI, whereas only 5% of patients without BBD had a breakthrough UTI. This report supported the findings of the study by Koff et al.[43] In another report, Chen et al. evaluated a database of 2759 children with UTI, VUR, or both, and found that 36% of girls with VUR had BBD and 21% of boys with VUR had BBD.[45]

The potential risk of BBD in a child with VUR is exemplified in a clinical case in Figure 43.2.

BBD in Infants

BBD in >2-year-old children is characterized by a combination of the following symptoms: urgency, urge incontinence, frequency, infrequent voiding, and constipation. In infants, however, parents typically are unaware of their child's toileting habits, unless they have significant constipation.

Sillén et al. evaluated the voiding pattern in 41 infants with grades III–V VUR using a noninvasive 4-hourly voiding record.[46,47] They found that 36% of boys voided frequently in small volumes, often with an uninterrupted stream, compared with 15% of the control group. Girls with moderate- and high-grade VUR typically were infrequent voiders. In addition, residual urine volume was significantly elevated in both boys and girls. The same group performed urodynamic studies in infants admitted to the hospital with clinical pyelonephritis.[48] Bladder instability was found in two-thirds of male and female infants. Compared with older children, male infants had a high voiding detrusor pressure and low bladder capacity. Female infants also had increased voiding pressure levels, but they were significantly lower than those in male infants. The voiding detrusor pressure was even higher in both sexes when evaluation was delayed after the UTI.

In a subsequent study, 89 males and 25 females with grades III–V dilating VUR underwent three videocystometric studies at mean ages of 6, 20, and 40 months.[49] They found that the voiding pattern at 6 months was similar in infants with VUR and controls. However, at 20 months, bladder dysfunction was seen in 48 children (42%), of whom 34 primarily had high bladder capacity with incomplete emptying ("dilated bladder dysfunction") and 14 had an overactive bladder. Predictors for development of dilated bladder dysfunction were high residual urine at 6 months and recurrent UTIs. Recurrent UTIs were significantly correlated to high residual urine at all investigations and to detrusor overactivity at the 20-month examination.

In summary, nearly half of infants with dilating VUR have dysfunctional voiding, including enlarged bladder capacity, overactive bladder, and incomplete bladder emptying; bowel dysfunction has not been systematically assessed in this patient population. Breakthrough UTIs occur most commonly in affected infants.

Medical Risks in Children with VUR and BBD

Few prospective trials have been conducted in children with VUR and BBD. However, children with VUR need to be assessed for BBD because the association of these conditions increases the risk for VUR-related complications. In addition, BBD in children with VUR requires directed therapy.

In the Swedish Reflux Trial, 203 children age 1–2 years with grades III and IV VUR were randomly assigned to receive antibiotic prophylaxis, subureteral injection therapy, or observation and were monitored for a period of 2 years.[50] At study entry, 20% of patients had lower urinary tract dysfunction characterized by high bladder capacity and increased postvoid residual urine volume.[51] After 2 years of follow-up, BBD was evident in 34% of all patients. Overall, 9% had an overactive bladder and 24% had voiding phase dysfunction. Those with voiding phase dysfunction at 2 years were significantly less likely to have VUR resolution. Renal damage at study entry and at 2-year follow-up was significantly more common in patients with lower urinary tract dysfunction. Recurrent UTIs occurred in 33% of children with and 20% of those without BBD, but these differences did not reach statistical significance.[51] These results were similar to previous reports that indicated BBD increases the risk of breakthrough UTI in children with VUR.

The 2010 AUA Reflux Guidelines Committee performed the most comprehensive analysis of the association between BBD and VUR through to 2008.[29] The reports that were analyzed included 2039 children with VUR, 75% of whom were female and 32% of whom had a concurrent diagnosis of BBD. In children receiving CAP, spontaneous resolution rates were 31% for those with BBD and 61% for those without BBD (Figure 43.3). The incidence of UTI managed with CAP was 44% in children with BBD and 13% in those without BBD (Figure 43.4), indicating that BBD is a significant risk factor for UTI in children with VUR receiving CAP. In children with VUR treated

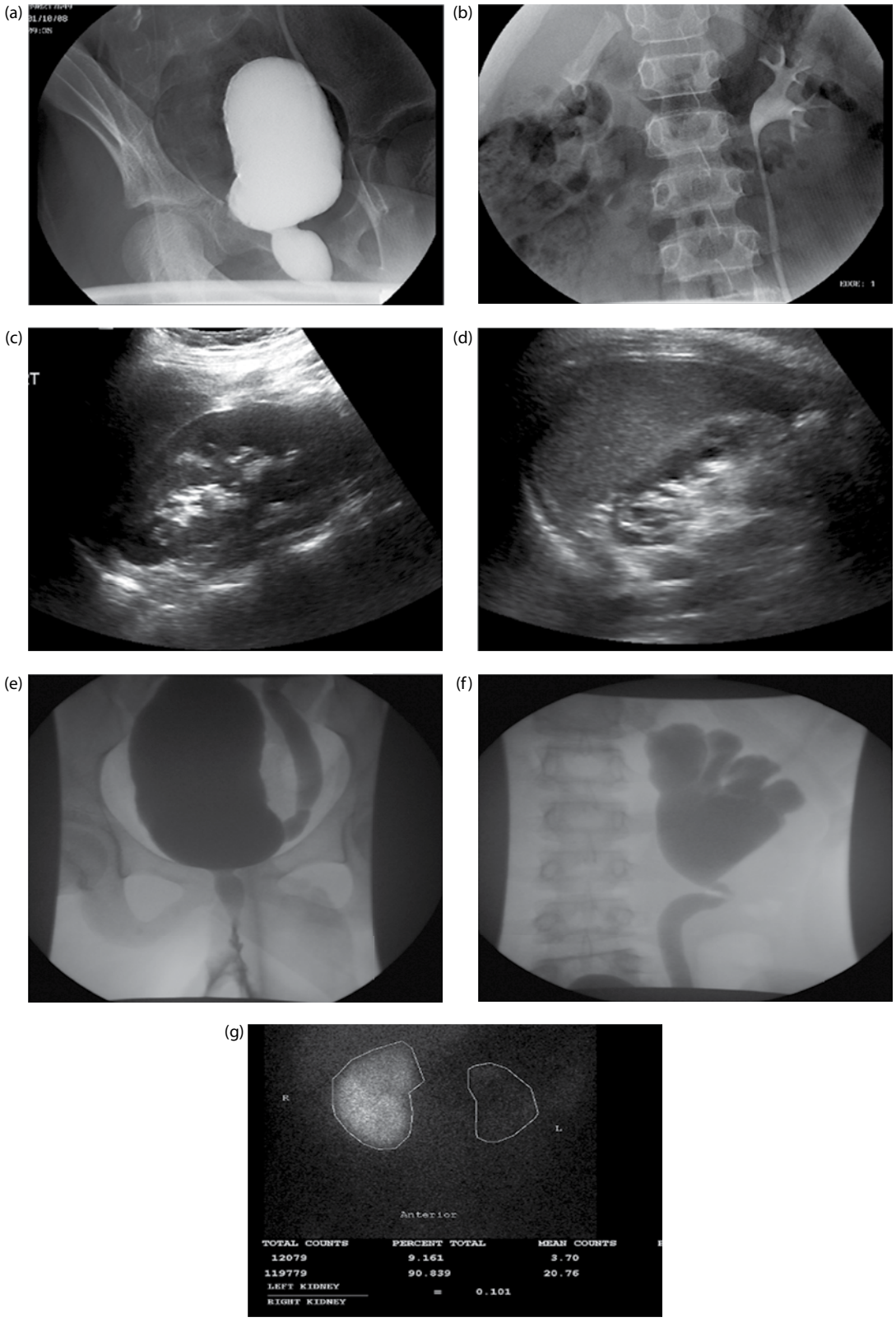

FIGURE 43.2 Six-year-old girl with BBD, with day and night incontinence and febrile UTIs. (a and b) A VCUG shows detrusor hypertrophy, "spinning top" deformity of urethra, and bilateral grade II or III VUR. Patient treated with antibiotic prophylaxis, bladder training, and anticholinergic therapy. Patient did not return for follow-up after age 7 years. At age 12 years, the child returned with recurrent febrile UTI and diurnal incontinence. (c and d) A renal sonogram shows a normal right kidney (c) and small irregular left kidney (d). (e and f) A VCUG shows detrusor hypertrophy and grade V left VUR with calyceal clubbing. (g) A DMSA renal scan shows a normal right kidney and minimal function in the left kidney.

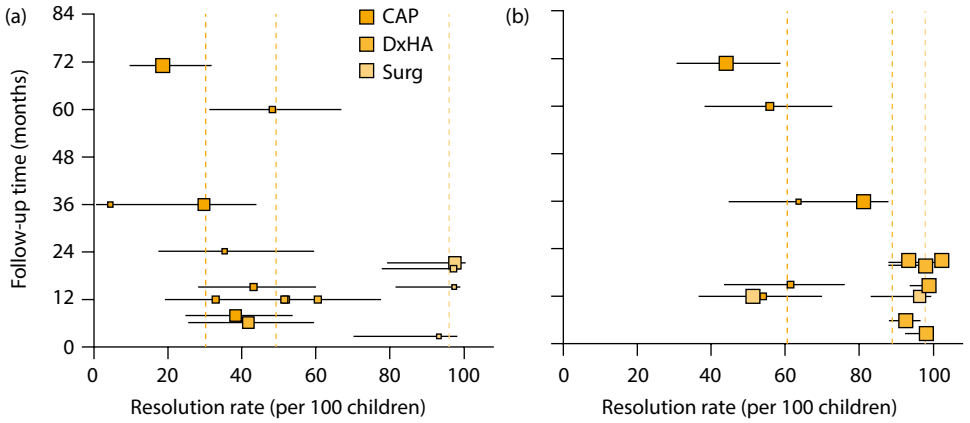

FIGURE 43.3 Forest plots comparing VUR resolution rates in children with (a) and without (b) BBD. DxHA = subureteral injection with dextranomer–hyaluronic acid copolymer; Surg = open surgery. Figures were drawn from data available from the AUA VUR guidelines. (Adapted from Peters CA et al. *J Urol* 2010;184:1134–44.)

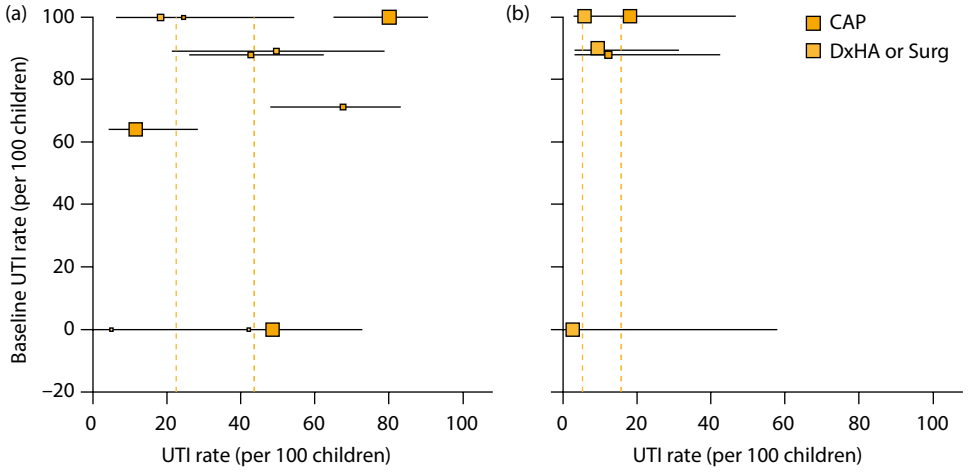

FIGURE 43.4 Forest plots comparing rates of UTI in children with (a) and without (b) BBD. DxHA = subureteral injection with dextranomer–hyaluronic acid copolymer; Surg = open surgery. Figures were drawn from data available from the AUA VUR guidelines. (Adapted from Peters CA et al. *J Urol* 2010;184:1134–44.)

surgically with subureteral injection therapy, resolution rates at 3–12 months were 50% for those with BBD and 89% for those without BBD (Figure 43.3). For children treated with open surgery, the presence of BBD did not alter the surgical resolution rate, which was 97% in both groups.[29] In each of these groups, the specific treatment method of BBD could not be assessed. Finally, the meta-analysis showed that the incidence of UTI was 22.6% for children with BBD and 4.8% for children without BBD following open or endoscopic surgical treatment, representing a statistically insignificant difference ($P = 0.08$); however, BBD outcomes were not stratified by sex, grade, or laterality for the BBD and non-BBD groups. More recent studies also have demonstrated that the rate of UTI following endoscopic injection therapy is higher in children with a history of BBD than in children without BBD (Table 43.3).

Based on these data, the 2010 AUA VUR guidelines recommend as a *standard* that symptoms indicative of BBD should be sought in the child's initial evaluation.

Evaluation for BBD in Children with VUR

Symptoms of BBD include urinary frequency and urgency, prolonged voiding intervals, daytime wetting, perineal or penile pain, holding maneuvers (posturing to prevent wetting), and constipation or encopresis (Table 43.4). Important points in the history include the pattern of incontinence, including the frequency, the volume of urine lost during incontinent episodes, whether the incontinence is associated with urgency or giggling, whether it occurs after voiding, and whether it is continuous. The frequency of voiding and whether there is nocturnal enuresis; a strong, continuous urinary stream; or sensation of incomplete bladder emptying should be assessed. Bowel habits also should be evaluated, because incontinence is common in children with constipation and/or encopresis. Physical examination is directed at identifying signs of organic causes of incontinence: short stature, hypertension, enlarged kidneys and/or bladder, constipation, labial adhesion, ureteral ectopy, back or sacral anomalies, and neurologic abnormalities.

TABLE 43.3 Studies of VUR in patients with or without VUR, 2008–2014

Study	VUR intervention	BBD intervention	Duration of treatment	Incidence of UTI in patients	
				With BBD	Without BBD
Chi et al.[52]	Dextranomer–hyaluronic acid injection therapy	Anticholinergic, bladder training, stool softeners	Median 32 months	17/39 (44%)	12/58 (21%)
Dwyer et al.[53]	Dextranomer–hyaluronic acid injection therapy	Anticholinergic, bladder training, stool softeners	Median 28 months	12/48 (24%)	5/58 (9%)
Sedberry-Ross et al.[54]	Dextranomer–hyaluronic acid injection therapy	NR	Mean 10 months	9/18 (50%)	9/27 (33%)
Sjöström et al.[49]	Continuous antibiotic prophylaxis	NR	Mean 19 months	37/48 (77%)	10/35 (28%)
Traxel et al.[55]	Dextranomer–hyaluronic acid injecion therapy	Bladder training	Mean 31 months	32/64 (50%)	8/247 (3%)
Whittam et al.[56]	Dextranomer–hyaluronic acid injection therapy	Anticholinergics, bladder training, stool softeners	Mean 15 months	5/58 (9%)	13/282 (5%)

Abbreviation: NR, no recommendation.

TABLE 43.4 Evaluation and management of bladder–bowel dysfunction

Clinical aspects	Urinary	Bowel
Signs and symptoms	Increased or decreased urinary frequency Daytime incontinence Urgency Nocturia Hesitancy Straining Weak stream Intermittent stream Holding maneuvers Sensation of incomplete voiding Postvoid dribbling	Two or fewer defecations per week ≥1 episode per week of stool incontinence Excessive stool retention Painful or hard bowel movements Large fecal mass in the rectum Large-diameter stool that blocks the toilet
Evaluation	Physical examination Bladder diary Pediatric Symptom Checklist Uroflow[a] Invasive urodynamics 4-hour voiding observation (infants) 24-hour fluid consumption and urine volume Voiding cystourethrogram	Abdominal x-ray Pelvic ultrasonography Spinal MRI
Management	Behavioral modification (e.g., timed voiding, bladder diary) Alarm therapy Biofeedback Sacral neuromodulation Pharmacologic (e.g., anticholinergic, alpha-blocker) Intermittent catheterization Antimicrobial prophylaxis (if recurrent UTI)	Education and behavioral modification Disimpaction Dietary intervention Oral laxatives Enemas Behavioral therapy and biofeedback

[a] Postvoid residual urine volume, flow rate, and flow curve shape.

Assessment tools should include urinalysis, with culture if indicated. In addition, a bladder diary, post-void residual urine volume (generally obtained by bladder scan), Dysfunctional Voiding Symptom Score (Figure 43.5), Bristol Stool Form Score (Figure 43.6), and uroflow with or without Electromyography (EMG) (patch electrodes) (patch electrodes) may be useful.

To help assess whether voiding dysfunction (BBD) is present, Farhat et al. reported a validated Dysfunctional Voiding Scoring System (DVSS), which consists of 10 questions pertaining to urinary and bowel habits.[57] Subsequently, this group applied the DVSS to children with reflux in a retrospective study. In children with a high symptom score managed with behavioral modification, those with a significant reduction in symptom score were most likely to show reflux resolution or improvement, whereas those with only a minor reduction in symptom score tended to have persistent reflux.[58] Prospective trials of this type of scoring system are necessary.

Bladder Diary

A record or diary of when the child voids and whether the child was wet or dry before voiding can also be helpful. Indeed, the 14-day bladder diary is useful in children of >5 years of age and in children who have achieved bladder control.[37] Important information recorded in the diary includes frequency of diurnal incontinence, frequency of daytime voiding, frequency of nocturia, severity of nocturnal enuresis, fluid intake volume and time, when the child goes to sleep and wakes up, frequency of defecation, and severity of encopresis.

Assessment of Bowel Function

Until recently, assessment of stool habits was based on the Bristol Stool Scale, in conjunction with stool frequency. The definition and diagnosis of functional constipation have evolved recently, following an international consensus (Rome III) for assessing this disorder.[59] Some urologists use the Rome III diagnostic criteria, which classify

Appendix 1 – *Original dysfunctional voiding symptom score.*

Over the Last Month	Almost Never	Less than Half the Time	About Half the Time	Almost Every Time	Not Available
1 - I have had wet clothes or wet underwear during the day.	0	1	2	3	NA
2 - When I wet myself, underwear is soaked.	0	1	2	3	NA
3 - I miss having a bowel movement every day.	0	1	2	3	NA
4 - I have to push for my bowel movements to come out.	0	1	2	3	NA
5 - I only go to the bathroom one or two times each day.	0	1	2	3	NA
6 - I can hold onto my pee by crossing my legs, squatting or doing the "pee dance".	0	1	2	3	NA
7 - When I have to pee. I cannot wait.	0	1	2	3	NA
8 - I have to push to pee.	0	1	2	3	NA
9 - When I pee, it hurts.	0	1	2	3	NA
10 - Parents to answer. Has your child experienced something stressful such as the examples below?		NO (0)			YES (3)
• New baby.					
• New home.					
• New school.					
• School problems.					
• Abuse (sexual/physical).					
• Home problems (divorce/death).					
• Special events (birthday).					
• Accident/injury.					
• Others.					
Total					

FIGURE 43.5 Dysfunctional Voiding Symptom Score. (Adapted from Farhat W et al. *J Urol* 2000;164:1011–15.)

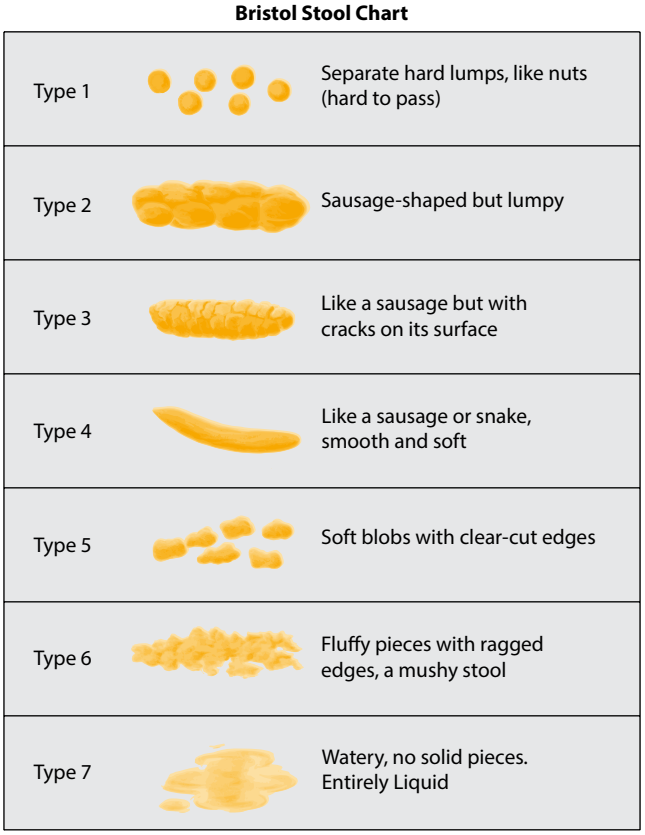

FIGURE 43.6 Bristol Stool Scale.

functional gastrointestinal disorders that do not have underlying structural or tissue-based causes.[60] Children of ≥4 years of age are diagnosed as being constipated if they fulfill two or more of the following criteria over a period of 2 months: two or fewer defecations in the toilet per week, at least one episode of fecal incontinence per week, a history of retentive posturing or excessive volitional stool retention, a history of painful or hard bowel movements, the presence of a large fecal mass in the rectum, and a history of large-diameter stools that obstruct the toilet.[59,61] In 2013, the ICCS published a report on the evaluation and management of functional constipation in children with lower urinary tract symptoms.[62] They recommended a complete history (including assessment of lower urinary tract symptoms and constipation) and physical, a urinalysis, a 7-day bowel diary, and measurement of postvoid residual urine volume, rectal diameter, and bladder wall thickness. For complex cases, they recommended evaluation by a pediatric gastroenterologist (colonic transit measurement, spinal MRI, defecography, and anorectal manometry). Encopresis was not addressed in this document, but is presumably a severe form of functional constipation.

Pediatric Symptom Checklist

The Pediatric Symptom Checklist (PSC) consists of 35 questions pertaining to cognitive, emotional, and behavioral problems experienced by the child; it may also be helpful in assessing external factors contributing to BBD. The questionnaire can be filled out by the parent or by both parent and child.[63,64] Those with a high overall PSC score may be referred to a pediatric clinical psychologist for evaluation and treatment, particularly if they are not already under the care of a neurologist. In addition, the Parenting Stress Index/Short Form (PSI/SF) may be useful in children who are refractory to conventional treatment. In addition, there is evidence that bullying might contribute to pediatric BBD.[65,66]

Urodynamic Tests

Noninvasive Urodynamic Tests

Uroflow

Measurement of urine flow and residual urine volume is an important diagnostic study, and consideration should be given to repeating these measurements once or twice to be certain that the results are consistent. Furthermore, pelvic floor electromyography is quite useful during uroflow to demonstrate sphincter relaxation during micturition (normal) or sphincteric contraction during micturition (indicative of detrusor sphincter discoordination).

The maximum flow rate is the most relevant variable and should be based on peak flow rates that have a duration of at least 2 seconds.[37] In healthy children and adults, a linear correlation between maximum flow and the square root of voided volume has been reported.[67] For example, if the square of the maximum flow is equal to or exceeds the voided volume in milliliters, the recorded maximum flow is probably within the normal range. Furthermore, the normal voiding curve is smooth and bell shaped, but in children with bladder outlet obstruction, a plateau curve of low amplitude can be recorded. If the patient has sphincter overactivity during voiding, a staccato flow curve is recorded, termed a continuous but fluctuating flow curve. In a staccato flow curve, the fluctuations should be larger than the square root of the maximum flow rate.[37]

In children, the postvoid urine volume might not consistently be <10% of bladder capacity, as it is in healthy adults, but the bladder should empty to this level at least once during a 4-hour observational period.[68] A volume of >20 mL on repetitive occasions suggests incomplete emptying, assuming the child has not waited too long before voiding. A persistent elevated postvoid residual urine volume is suggestive of BBD, but is also observed in boys with a urethral stricture.

An important urodynamic measurement to evaluate detrusor function in infancy is the 4-hourly voiding observation. This assessment involves continuous observation of a freely moving infant with frequent ultrasonography measurements of bladder filling and measurement of residual urine after each micturition. Voided volume can be measured by weighing the infant's diaper.[46]

Invasive Urodynamic Tests

Urodynamic assessment (or videourodynamics) should be performed if the child has symptoms of detrusor sphincter discoordination (such as intermittent stream, slow stream, or incomplete bladder emptying), and if he or she does not respond to empirical treatment (European Association

of Urology [EAU] recommendation).[69] The voiding cystourethrogram (VCUG) should be inspected carefully for evidence of detrusor sphincter discoordination, with the presence of a dilated urethra proximal to the sphincter (the so-called spinning top deformity) in both girls and boys (Figure 43.2a).[70] If the patient has VUR of grade III or higher, a DMSA renal scan is indicated to determine whether the child has renal scarring.

An appropriate filling rate is 5% of the expected bladder capacity per minute.[71] The expected bladder capacity (mL) is approximately (Age [in years] + 2) × 30. With regard to bladder sensation, decreased bladder sensation during bladder filling is suggestive of detrusor underactivity.[37] However, unlike older children and adolescents, children of <5 years are only able to express a strong desire to void. Instead, nonverbal signs of bladder sensation must be interpreted, which include holding maneuvers such as toe curling and leg movements.

In a normal urodynamic study, little or no change in pressure is evident during bladder filling and no involuntary bladder contractions occur. In contrast, detrusor overactivity is characterized by involuntary contractions involving an increase of >15 cmH_2O in detrusor pressure above baseline. In normal children, a detrusor pressure of 10 cmH_2O at expected bladder capacity is appropriate, and when bladder capacity is reached, the child experiences considerable suprapubic discomfort. Bladder compliance is an indication of detrusor hypertrophy and is calculated by dividing the volume change by the change in detrusor pressure, and is expressed in milliliters per cmH_2O. However, no reliable reference values for bladder compliance in infancy and childhood are available; in general, detrusor pressure should be 10 cmH_2O at expected bladder capacity for age. The elevated bladder compliance typically is observed in children with neuropathic bladder, valve bladder syndrome, and Hinman syndrome.

To investigate the role of urodynamic assessments in children with VUR and suspected BBD, Ramamurthy and Kanitkar prospectively analyzed the results of history, physical examination, voiding diary, urinalysis, sonography, and renal function tests, and compared these with invasive urodynamics in 41 children.[72] They reported a sensitivity of 88% and specificity of 73% with the noninvasive approach, suggesting that the invasive tests should be reserved for children with complex voiding disorders or those who are resistant to conventional therapy.

MANAGING PATIENTS WITH BBD AND VUR (TABLE 43.4)

The management of children with VUR and BBD should be individualized. Currently, no randomized trials have compared children with VUR and BBD receiving treatment with those not receiving specific treatment for BBD. Despite this fact, both the 2010 AUA and 2015 EAU/ESPU (European Society for Paediatric Urology) guidelines agree that BBD should be treated in children with VUR.[29,69] For these reasons, comparison of medical treatment options is difficult.

Urotherapy (Bladder Training)

Bladder training refers to regular, volitional, complete emptying of the bladder through behavioral conditioning to achieve balanced, low-pressure voiding with coordinated relaxation of the external sphincter and pelvic floor during voiding. The goal of bladder training is to reduce the likelihood of developing UTI and reduce voiding pressure. Measures include a voiding schedule every 2–3 hours, complete bladder emptying during micturition, reeducation in proper voiding dynamics if voiding dysfunction is present, and elimination of constipation. The practice also includes genital and perineal hygiene. Although these recommendations are practical, no firm evidence exists that a specific regimen is beneficial.

Bowel Management

Aggressive treatment of constipation is the first step in dealing with BBD. Typically, in these children, maintenance treatment with polyethylene glycol powder dissolved in water or juice is prescribed once daily, to stimulate a soft bowel movement each day. Compliance with this regimen is inconsistent because of side effects, and concern by the parents that the child might experience encopresis at school. Alternatives include other osmotic oral laxatives (lactulose and magnesium hydroxide), a lubricant laxative (mineral oil), or stimulants (orally or rectally administered bisacodyl or senna). Some have questioned the effectiveness of polyethylene glycol treatment. For example, Bush et al. reported that in a series of 138 children with urinary urge symptoms randomly assigned to empiric polyethylene glycol or placebo, 50% showed improvement in urge symptoms after 1 month of treatment in both groups.[73] In addition, they observed that the plain abdominal film used to assess stool retention did not correlate with baseline or follow-up bowel or urinary symptoms. On the other hand, Champeau and Baskin suggested that all children with lower urinary tract symptoms are constipated and should be treated accordingly.[74] This recommendation was based on the fact that five of the six Rome III criteria are based on patient history, and emphasize that patient history provided by parents is often inaccurate.

Biofeedback

In children with BBD, typically there is inconsistent relaxation of the external sphincter during voiding. This pattern may occur because of repeated unstable bladder contractions that cause the child to tighten his or her sphincter, as opposed to the normal pattern, in which the sphincter is relaxed during a detrusor contraction. Many of these children demonstrate a staccato voiding pattern on a uroflow study. Biofeedback may be useful, not only to establish a normal pattern of sphincteric relaxation during voiding, but also to eliminate or reduce the need for anticholinergic medication for the overactive bladder. A typical treatment session might include a uroflow study, sonographic evaluation of postvoid residual urine volume, and a 1-hour session with perineal patch electrodes for EMG. The child watches the sphincter activity on a television screen and learns to contract and relax his or her external sphincter,

essentially Kegel exercises. In addition to this simple office setup, video games have been developed that help the child coordinate his or her sphincter tone.[75] An alternative is to simply teach the child pelvic floor exercises without using sophisticated urodynamic equipment.[76]

The concept of biofeedback is that children may have difficulty isolating their external sphincter, and biofeedback sessions allow them to learn sphincteric relaxation, which is necessary as a prerequisite to normal bladder emptying. In addition, pelvic floor exercises may also ameliorate unstable bladder contractions. Children should perform these exercises daily, although no formal regimen is used. Several weekly or monthly sessions are necessary to reinforce the importance of the treatment, as well as determine whether voiding patterns are improving and whether residual urine volumes are decreasing. Subsequently, the sessions can be spaced farther apart.

Most reports of biofeedback for the management of voiding dysfunction have been favorable. Some utilize biofeedback in children with symptoms of an overactive bladder that do not respond to anticholinergic therapy and timed voiding, while others use it as an alternative to anticholinergic medication. However, it is uncertain how often anticholinergic therapy can be reduced or eliminated in children with an overactive bladder. Some centers have reported that the need for antireflux surgery was eliminated in many cases,[75] and that the rate of reflux resolution was higher in children submitted to biofeedback.[77] Furthermore, animated biofeedback with video games has been reported to be more effective than nonanimated biofeedback.[78]

Although reports of biofeedback have demonstrated success, many patients undergoing treatment have also been receiving pharmacologic therapy, making it difficult to accurately assess the benefit of biofeedback. One problem when comparing these studies is that inclusion criteria for clinical trials regarding BBD and treatments are inconsistent. The preferences and situations of the families can also influence the kinds of treatments that can feasibly be offered to the patients. For example, some families live far away from biofeedback centers and are unable to make the multiple appointments. In addition, some families prefer to avoid medications, or if medications are prescribed, compliance or adherence might be inconsistent. These issues often occur in families where the child stays in two different homes and the parents have disagreed on the need for treatment.

DeSantis et al. performed a systematic review of reports on biofeedback in patients with BBD with or without VUR.[79] Of the 27 studies included in the review, only one was a randomized controlled trial. Overall, the reduction in UTI was 83% and the improvement in diurnal incontinence 80%. More recently, Fazeli et al. performed a meta-analysis of five randomized controlled trials and was unable to demonstrate any benefit from biofeedback.[80] In their analysis, the rate of resolved incontinence, maximum urinary flow, and UTI was similar in both treatment groups and controls. The authors pointed out that the clinical responses were often short-lived, 6 or 12 months, with little or no mention of longer-term successes. The main issue is that this therapy is recommended as a cookbook approach that is not tailored to specific sets of symptoms. Children with incomplete emptying from infrequent urination often have an abnormal flow pattern that increases the risk of UTI, and they may need a different form of therapy compared with children with diurnal incontinence secondary to a small bladder capacity or overactive bladder. The former require instruction in pelvic floor (external urethral sphincter) relaxation, while the latter need to learn tightening techniques when they have the urge to void in response to detrusor overactivity.

Pharmacologic Therapy

Anticholinergic Therapy

Children with an overactive bladder typically have urgency, frequency, and/or urge incontinence. When girls with this condition sense a sudden bladder contraction, they often cross their legs or squat down on their foot to try to prevent incontinence. In these children, a combination of anticholinergic therapy and timed voiding may be beneficial.[81] The anticholinergic is administered according to the incontinence pattern of the specific child. Most children with an overactive bladder experience incontinence throughout the day and night, and these children should receive the medication so that the effect lasts 24 hours. Other children may be incontinent only during the day, and these children do not need nighttime medication. Typically, 2.5–5 mg of oxybutynin chloride tid is prescribed initially, as it is the only antimuscarinic medication approved for use in children. The medication is available as a tablet or suspension. Typical side effects include xerostomia (dry mouth), facial flushing, reduced sweating, and constipation, and less commonly blurred vision and drowsiness. Side effects are dose related and may be eliminated with dose reduction, or with the extended-release or transdermal patch. Other antimuscarinics include hyoscyamine, which is available as a sublingual tablet, 0.125–0.25 mg qid, or as a capsule taken twice daily; tolterodine 1–2 mg bid; trospium 10–25 mg daily in two doses; darifenacin; solifenacin;[82,83] and propiverine (not available in the United States).[84,85] In children with an overactive bladder who fail urotherapy, anticholinergics can result in diurnal dryness in as many as 80%.[86] These medications have the same potential for side effects as oxybutynin, but their incidence and severity are less. Oxybutynin and tolterodine may affect attention span and short-term memory in elderly patients, but these side effects have not been observed in children.[87] Although these medications are not specifically approved for use in children, they are utilized in many centers, but their dosage and timing of administration need to be individualized and closely monitored. In children receiving an anticholinergic with persistent diurnal incontinence, combining two different medications ("double anticholinergic") has a significant likelihood of achieving dryness.[88] The beneficial effect attributed to anticholinergic medications may be due in part to a placebo effect, as in phase 3 clinical trials many patients achieve dryness on the placebo arm. On the other hand, anticholinergic therapy should be considered a therapeutic modality in children with VUR and an overactive bladder, in that there is an increased likelihood of spontaneous reflux resolution in children

treated with anticholinergics, in addition to its reduction in diurnal incontinence.[39,42]

Alpha-Blocker Therapy

Some children with BBD have pelvic floor overactivity and have significant postvoid residual urine volumes. These children may benefit from alpha-blocker therapy. In a prospective randomized double-blind trial of 38 children, Kramer et al. found that 0.5 mg of doxazosin resulted in a dramatic reduction in incontinence episodes, compared with no change in the placebo group.[89] The differences were not statistically significant, because of small patient numbers. There was significant subjective improvement, however, in the children receiving doxazosin. In a more recent trial of 62 children with VUR and bladder neck dysfunction treated with prazosin or placebo, there was a significant reduction in VUR grade, postvoid residual urine volume, and average flow rate.[90]

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CHAPTER
44

Surgery for Vesicoureteral Reflux

John W. Brock III and Douglass B. Clayton

INTRODUCTION

Multiple techniques for the open surgical repair of vesicoureteral reflux (VUR) have been described since Hutch first reported the successful correction of VUR in 1952.[1] Although many methods have been proposed, most of these techniques have become footnotes in the evolution of the surgical management of VUR. Today, most surgeons employ only a handful of the previously described repairs.

The surgical correction of VUR has as its goal the restoration of the flap valve mechanism absent in children with reflux. Success using any of the described open techniques requires adherence to the general surgical principles of proper tissue handling and preservation of tissue vascularity. Specific surgical tenets of ureteral reimplantation surgery include the establishment of an adequate submucosal tunnel, a smooth course for the intravesical ureter, and an adequate posterior bladder wall for submucosal tunnel backing. Despite the emergence of less invasive alternatives to antireflux surgery, open surgical repair of VUR continues to be the "gold standard" against which all other methods are measured.

HISTORICAL BACKGROUND

The earliest descriptions of ureteral reimplantation surgery appeared in the medical literature near the turn of the twentieth century. The first reported ureteroneocystostomy is credited to Tauffer in 1877 by Bovee in a review article on ureteral surgery in 1900.[2] Bovee described 80 cases of ureteral reimplant surgeries, the vast majority performed following accidental division of the ureter at the time of laparotomy for ureteral fistulae resulting from prolonged labor or forceps delivery. Subsequently, other innovative procedures for reimplanting the ureter were described in the early part of the twentieth century unrelated to the treatment of VUR.[3–9]

In 1952, Hutch reported the successful correction of VUR in seven out of nine paraplegic patients with a combined extravesical and intravesical dissection.[1] Hodson followed with his findings that VUR was more common in children with urinary tract infections (UTIs), and that there was a high correlation between VUR and chronic pyelonephritis, as seen on intravenous pyelography (IVP).[10] These landmark papers led to further investigation into the treatment of VUR and played a pivotal role in the development of pediatric urology as a separate subspecialty.

Following Hutch's seminal paper, many surgical techniques were described. Landmark refinements of Hutch's operation included Politano and Leadbetter's technique of intravesical mobilization of the terminal ureter with subsequent reimplantation through a new vesical hiatus and submucosal tunnel.[11] Paquin's method summarized several fundamental requirements of successful VUR surgery, including the creation of a tension-free ureteral anastomosis and a submucosal tunnel length five times longer than the diameter of the ureter.[12] An extravesical approach soon followed, with almost simultaneously reported techniques described by Lich and colleagues in the United States and Gregoir and Van Regemorter in France in the early 1960s.[13,14] Glenn and Anderson reported success using their modified ureteral advancement technique without creating a new muscular hiatus in the mid-1960s.[15] Cohen subsequently modified the ureteral advancement procedure and achieved adequate submucosal tunnel length by using the posterior aspect of the bladder for cross-trigonal tunneling.[16] These descriptions, in addition to contributions by other surgeons over the last 50 years, have made open surgical correction of VUR an effective and durable surgical treatment.

INDICATIONS

The surgical indications for VUR should be tailored to the individual patient. However, standard indications for antireflux surgery have been generally accepted. Absolute indications for surgery include breakthrough UTIs despite prophylactic antibiotics or because of medical noncompliance. Relative indications for reimplant surgery include the following: persistent grade IV or V reflux, VUR associated with congenital abnormalities at the ureterovesical junction, renal growth retardation or the presence of new renal scars, and dilating reflux persisting in girls who have reached full somatic growth potential.

At Vanderbilt Children's Hospital (VCH), detailed counseling is initiated at the first clinic visit in patients referred to our office with concomitant diagnoses of UTI and VUR. Such counseling includes the importance of maintaining good voiding mechanics, adhering to daily antibiotic suppression, and avoiding bladder–bowel dysfunction. These issues are repeatedly stressed to both the patient and the parents. If indications for surgical

intervention are present, other factors to consider include the nature of the infections while on medical therapy, possible neurologic or nonneurologic bladder dysfunction, and the presence of bladder–bowel dysfunction. Informed operative consent and expectations following surgery are explained in detail to both the parents and the child.

The evaluation and management of pediatric patients with UTI and VUR has changed dramatically over the last decade, as will be discussed at length in Chapter 43. Undoubtedly, restricting the use of voiding cystourethrography (VCUG) in younger children with febrile UTI, as recommended by the American Academy of Pediatrics in 2011, will impact the specialty of pediatric urology.[17] As fewer children undergo VCUG for febrile UTI following the release of these guidelines, the impact on subsequent surgical management remains unclear. Likely, the practice patterns for treating VUR both medically and surgically will change and surgical intervention may decline over time. At VCH, our practice patterns have remained stable in that we continue to primarily perform open ureteral reimplantation for antireflux surgery compared with endoscopic procedures. The release of new guidelines is unlikely to change this fact. Despite the evolving nature of VUR screening, evaluation, and management, open surgery for VUR remains a safe and effective procedure for children in whom it is indicated.

SURGICAL TECHNIQUES

Cystoscopy

Cystoscopy may be performed prior to open ureteral reimplantation surgery following induction of general anesthesia. Cystoscopy should take only a few minutes from positioning to completion. It alerts the surgeon to unexpected anatomical findings not found on preoperative imaging studies. Duplication anomalies, the presence of small ureteroceles, or evidence of posterior urethral valves or other urethral abnormalities may be found. Bladder trabeculae are seen well during cystoscopy and may be related to voiding dysfunction. Additionally, acute cystitis, if found during endoscopy, delays open surgery until an appropriate course of antibiotic therapy has been completed.

However, cystoscopy is not mandatory in all patients and, with the improvement in diagnostic imaging techniques, typically adds little information. Male patients, those with unclear radiographic findings, or patients with anatomic abnormalities found on preoperative imaging studies are a few of the select group of patients who may benefit from endoscopy.

Positioning

If cystoscopy is performed, the bladder is left moderately distended. The child is then positioned supine and either a rolled towel is placed at the level of the upper sacrum, or a slight break in the table is used to raise the lower pelvis and hips (Figure 44.1a and b). All pressure points are appropriately padded, and a wide surgical prep is performed with the perineum draped and exposed within the surgical field (Figure 44.1c).

INTRAVESICAL TECHNIQUES

Exposure and Initial Dissection

Exposure for all methods of intravesical repair involves a series of similar steps before the individual techniques diverge during ureteral reimplantation. A Pfannenstiel skin incision is made along an appropriate skin crease about one fingerbreadth above the pubic symphysis (Figure 44.2a and b). The subcutaneous tissue and Scarpa's fascia are incised the length of the skin incision (Figure 44.2c). The anterior rectus sheath is then opened in a horizontal fashion (Figure 44.3a) with the creation of superior and inferior rectus flaps (Figure 44.3b). The rectus muscle bellies are then incised in the midline through the linea alba, separating the rectus and the pyramidalis muscle (Figure 44.3c). Alternatively, the anterior rectus fascia can be opened in a vertical fashion, extending the incision posteriorly through the linea alba.

Following the fascial incision, the space of Retzius is entered bluntly. The peritoneal reflection is displaced superiorly, the bladder is visualized, and full-thickness bladder wall stay sutures, or Allis clamps, are placed on either side of the midline of the bladder. The Denis Browne retractor is a helpful aid in allowing for sustained exposure and is used extensively at VCH. The anterior bladder wall is then incised longitudinally, and the inferior edges of the bladder wall are sewn to the lower

FIGURE 44.1 (a) Lateral view of the patient prior to prepping and draping. (b) Anterior view of the patient just prior to prepping and draping. (c) Wide surgical prep including the genitalia. (Photos courtesy of Anne Raynor, Vanderbilt University Medical Center, Nashville, Tennessee.)

FIGURE 44.2 (a) Proposed Pfannenstiel incision marked one fingerbreadth above the pubic symphysis. (b) Incision of the skin and subcutaneous tissue. (c) Careful dissection through Scarpa's fascia to expose the anterior rectus sheath. (Photos courtesy of Anne Raynor, Vanderbilt University Medical Center, Nashville, Tennessee.)

abdominal skin edges, immobilizing the inferior aspect of the bladder (Figure 44.4a). Moist sponges are packed in the dome of the bladder behind the cephalad blade retractor to flatten the posterior bladder wall and elevate the entire bladder in the pelvis, bringing the ureteral orifices into the middle of the operative field. Lateral blades are secured to the Denis Browne to obtain further exposure (Figure 44.4b). Optimal exposure involves the immobilization of the inferior aspect of the bladder, flattening of the posterior bladder wall, and elevation of the bladder into the pelvis, bringing the ureteral orifices into the middle of the operating field. Care must be taken during positioning of the Denis Browne blades to prevent tearing of the bladder incision through the bladder neck region. Also, excessive touching, suctioning, or rubbing of the bladder mucosa is avoided to prevent edema or inflammation of the mucosa, which can lead to bleeding and difficult mucosal dissection.

Ureteral dissection begins with intubation of the ureter with either a 5 or 3 French feeding tube, depending on the size of the ureteral orifice (Figure 44.5a and b). The tube is secured to the ureter with a 4-0 silk suture placed in a transverse fashion just inferior to the ureteral orifice, and then through the feeding tube, which maintains orientation of the ureter throughout mobilization (Figure 44.5c). The mucosa is then circumferentially incised around the ureteral orifice with the electrocautery in the cutting mode, leaving a several-millimeter cuff of bladder mucosa (Figure 44.6a). The muscular attachments of the ureter to the bladder are then carefully divided with the electrocautery device using the coagulation mode. This dissection involves gentle countertraction of the ureter away from the periureteral tissue using the feeding tube, in concert with judicious use of the cautery device (Figure 44.6b). Care is taken to avoid both devascularization and injury to the continuity of the ureter. The appropriate plane of dissection is achieved if the shiny, reflective ureteral wall in Waldeyer's sheath is seen. As the dissection proceeds proximally, division of the ureteral attachments is taken down further from the ureter to avoid devascularization. Ureteral dissection ends after an adequate distance of the ureter has been freed. A good measure of this distance is for the ureter to have enough length to reach the contralateral bladder wall. An additional clue is the subtle feeling of ureteral release the experienced surgeon is alert to, which allows the redundant ureter to easily slide back and forth in the muscular hiatus (Figure 44.6c).

Politano–Leadbetter Repair

The original Politano–Leadbetter technique described in 1958 involved the blind creation of a new suprahiatal muscular location for the ureter.[11] Following adequate ureteral mobilization as described above, the peritoneum is reflected superiorly away from the posterior aspect of the bladder using the original muscular hiatus as a window in which to work through (Figure 44.7a). If the muscular opening is not adequate for exposure, the posterior bladder wall may be incised superiorly to allow for better visualization. Perivesical crossing vessels, when encountered during division of the bladder wall, are fulgurated. The posterior bladder wall dissection is done under direct

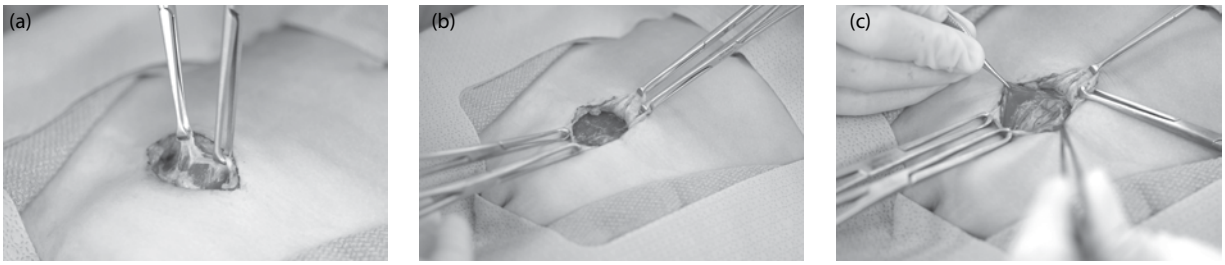


FIGURE 44.3 (a) Transverse fascial incision and development of superior fascial flaps aided by placement of two Allis clamps on the rectus fascia. Note the pyramidalis muscle in the midline. (b) Further proximal development of the superior fascial flap. (c) Entry into the space of Retzius by dividing the rectus muscle bellies in the midline to expose transversalis fascia overlying the bladder. (Photos courtesy of Anne Raynor, Vanderbilt University Medical Center, Nashville, Tennessee.)

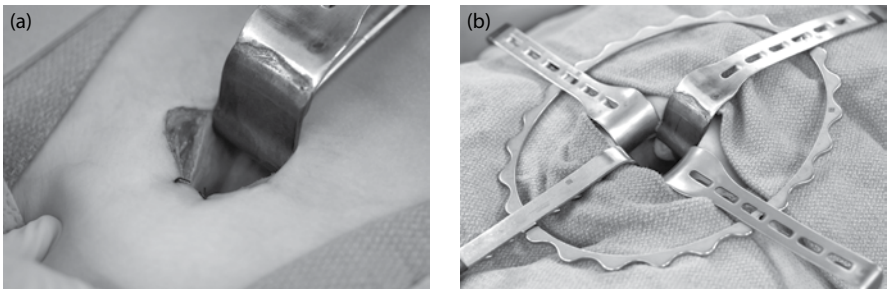


FIGURE 44.4 (a) A retractor is placed superiorly to expose the floor of the bladder and allow placement of a 3-0 silk suture through the bladder wall and skin of the lower incision. These sutures assist in elevating the bladder into the field. (b) The Denis Browne retractor is placed with a small curved blade used inferiorly and two bladder blades laterally. Superiorly, moist sponges packed in the dome and a Deaver blade help to elevate the floor of the bladder and improve visibility. (Photos courtesy of Anne Raynor, Vanderbilt University Medical Center, Nashville, Tennessee.)

visualization. Blind passage of instruments behind the bladder is forbidden because of the risk of unrecognized entry into the peritoneum or injury to the bowel, vagina, or vas deferens.

Once the posterior bladder wall is freed from the peritoneal reflection, a right-angle clamp is passed through the original hiatus superiorly under direct vision, hugging the posterior wall and indenting the bladder wall superiorly, marking the new muscular entrance for the ureter (Figure 44.7b). The location of the new hiatus is slightly medial and cephalad, typically 2–3 cm above the original hiatus. Excessive lateral placement allows for potential kinking and "J-hooking" of the ureter during bladder filling. The mucosa and muscle are incised directly on the right-angle clamp with the electrocautery device, and the right-angle tip is delivered into the bladder, dilating the opening carefully (Figure 44.7c). A second right-angle clamp is passed through the newly made hiatus inferiorly, and the ureter is then transferred to its new muscular hiatus, using the amputated feeding tube as a handle (Figure 44.7d–f). Careful relocation of the ureter involves ensuring a relatively smooth entrance of the ureter without acute angulations or kinks. The original muscular opening is then closed with 3-0 interrupted chromic sutures in a buried fashion. Adequate room for the ureter to emerge through the new hiatus is measured by the gentle insertion of the tip of a Schnidt clamp (Figure 44.7g).

A submucosal tunnel or mucosal flaps are created from the new entrance of the ureter toward a spot distally near the bladder neck, which is marked with the electrocautery. A modification of Politano and Leadbetter's original description involves increasing the submucosal tunnel length by extending the tunnel past the native ureteral orifice toward the bladder neck. Submucosal dissection is performed carefully with tenotomy scissors or the cautery device, and should proceed with ease through a bloodless field if in the correct plane (Figure 44.7f). Once an adequate submucosal tunnel has been made, the ureter is transferred through the tunnel (Figure 44.7h). The feeding tube is then removed, and the ureter is spatulated if needed. If excessive ureteral redundancy is present, the distal tip of the ureter may be excised. Three 6-0 vicryl sutures are placed through the posterior apex of the distal ureter and through both bladder mucosa and muscle to secure the ureter distally and prevent it from springing back into the tunnel. Then 6-0 vicryl mucosal sutures are placed circumferentially around the ureteral orifice, completing the mucosal anastomosis. The original mucosal opening is closed with fine absorbable suture, and if mucosal flaps were created, they are approximated with a running fine absorbable suture (Figure 44.7i). The bladder is then closed in two layers with a 3-0 chromic suture in a running fashion.

Cohen Cross-Trigonal Repair

Arguably, today's most popular open technique for ureteral reimplantation is the cross-trigonal repair described by Cohen in 1975.[16] Ureteral dissection is performed as described above; however, this method typically requires less ureteral mobilization than the Politano–Leadbetter

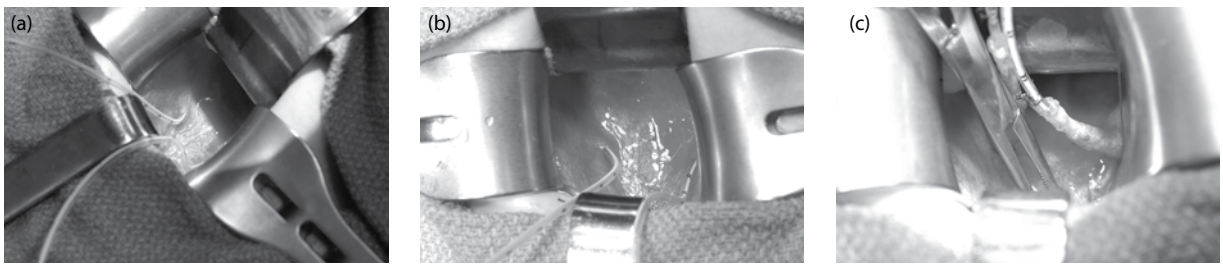


FIGURE 44.5 (a and b) With the Denis Browne retractor in place, 5 French feeding tubes are placed into the ureteral orifices to allow ureteral dissection to begin. (c) A 4-0 silk suture is used to secure the feeding tube at the orifice. The feeding tube is then used as a handle during dissection. (Photos courtesy of Anne Raynor, Vanderbilt University Medical Center, Nashville, Tennessee.)

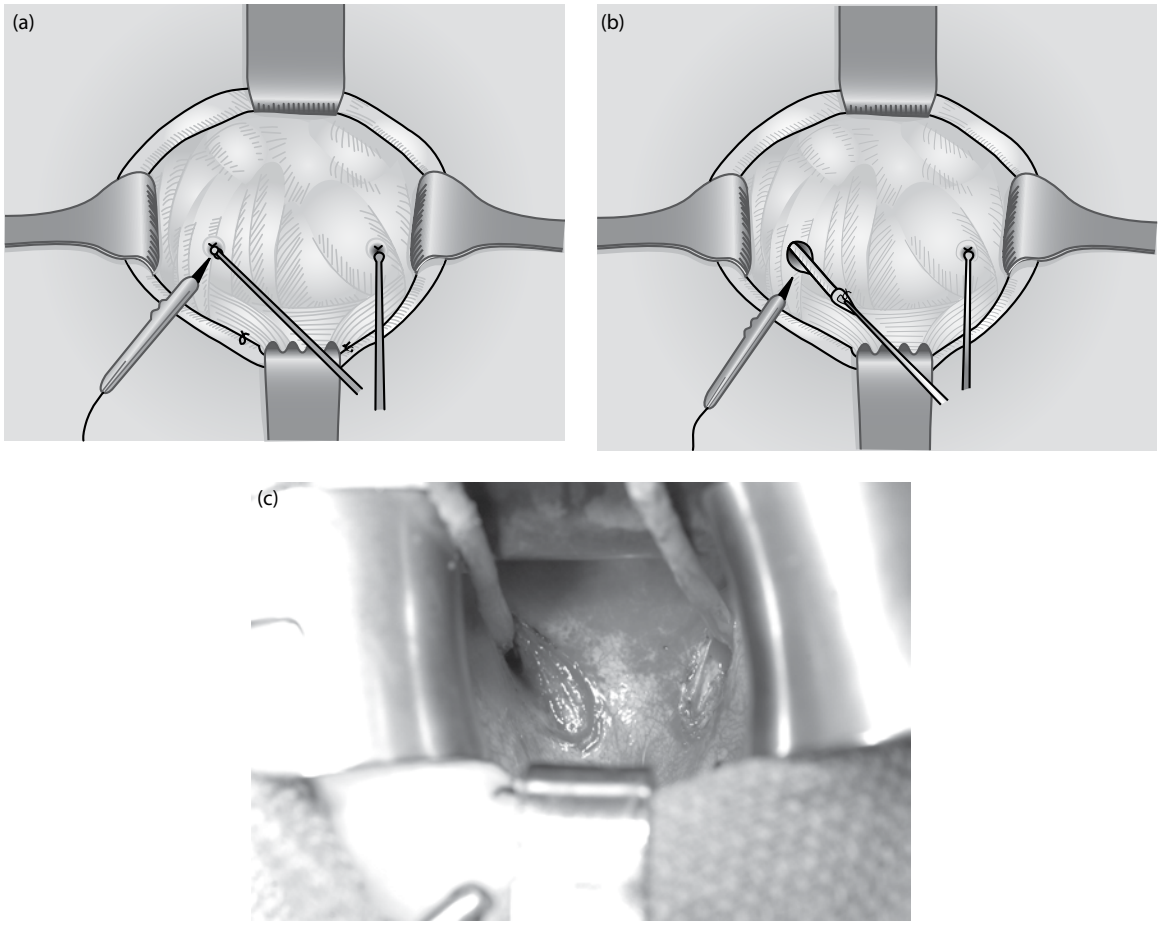


FIGURE 44.6 (a) The mucosa is incised circumferentially around the ureteral orifice with an electrocautery device. (b) The ureteral attachments are carefully divided, and an adequate ureteral length for reimplant is obtained. (c) Ureteral dissection has been completed bilaterally. Each ureter has been dissected well into the retroperitoneum, allowing sufficient redundancy of length. (Photo courtesy of Anne Raynor, Vanderbilt University Medical Center, Nashville, Tennessee.)

technique. The submucosal tunnel is created along the posterior bladder wall without transferring the ureter to a new muscular hiatus, virtually eliminating kinking of the distal ureter. The major drawback to this operation is the subsequent difficult intubation of the ureteral orifices related to their transtrigonal location. Despite this drawback, a number of authors have published techniques for facilitating endoscopic retrograde ureteral access after cross-trigonal reimplantation. Proposed techniques include the use of angle-tipped ureteral catheters, angled guidewires with torque devices, super stiff guidewires, and lateral percutaneous bladder puncture.[18–20]

Following ureteral mobilization, the muscular hiatus may need approximation if a patulous opening is present. Cinching of the hiatus with a 3-0 chromic suture should bring the muscle together tightly but allow for the tip of a Schnidt clamp to pass between the bladder and ureter. Aggressive closure of the muscular hiatus can cause kinking with angulation of the ureter and possible distal ureteral obstruction. In contrast, too lax of a muscular approximation may lead to diverticulum formation.

During unilateral ureteral reimplantation, a submucosal tunnel is developed across the posterior bladder wall in a cross-trigonal fashion. The new mucosal hiatus is created above the contralateral ureteral orifice. This ureteral position allows for an adequate submucosal tunnel. Once the submucosal tunnel is created, the ureter is transferred through the tunnel using the shortened feeding tube and stay suture as a handle. The feeding tube is then removed from the ureter. The ureter is spatulated, as indicated, and three fine absorbable sutures are placed through the lateral, posterior apex of the ureter and the bladder mucosa and muscle. Placement of these tacking sutures in the correct position creates an appropriate lateral vector force on the ureter, preventing medial regression of the ureter and loss of the effective submucosal tunnel. The newly created ureteral orifice is then matured with circumferential fine absorbable sutures. The mucosal defect from the old ureteral orifice is then closed with interrupted fine absorbable sutures (Figure 44.8a and b). Prior to closing the bladder, the free, smooth passage of a small feeding tube rules out excessive ureteral kinking.

When both ureters are reimplanted, the submucosal tunnel for the most superior ureter is made with the mucosal hiatus located just above the contralateral ureter. Subsequently, the other ureter is brought across the posterior bladder wall, with the new ureteral orifice positioned close to the inferior portion of the old contralateral

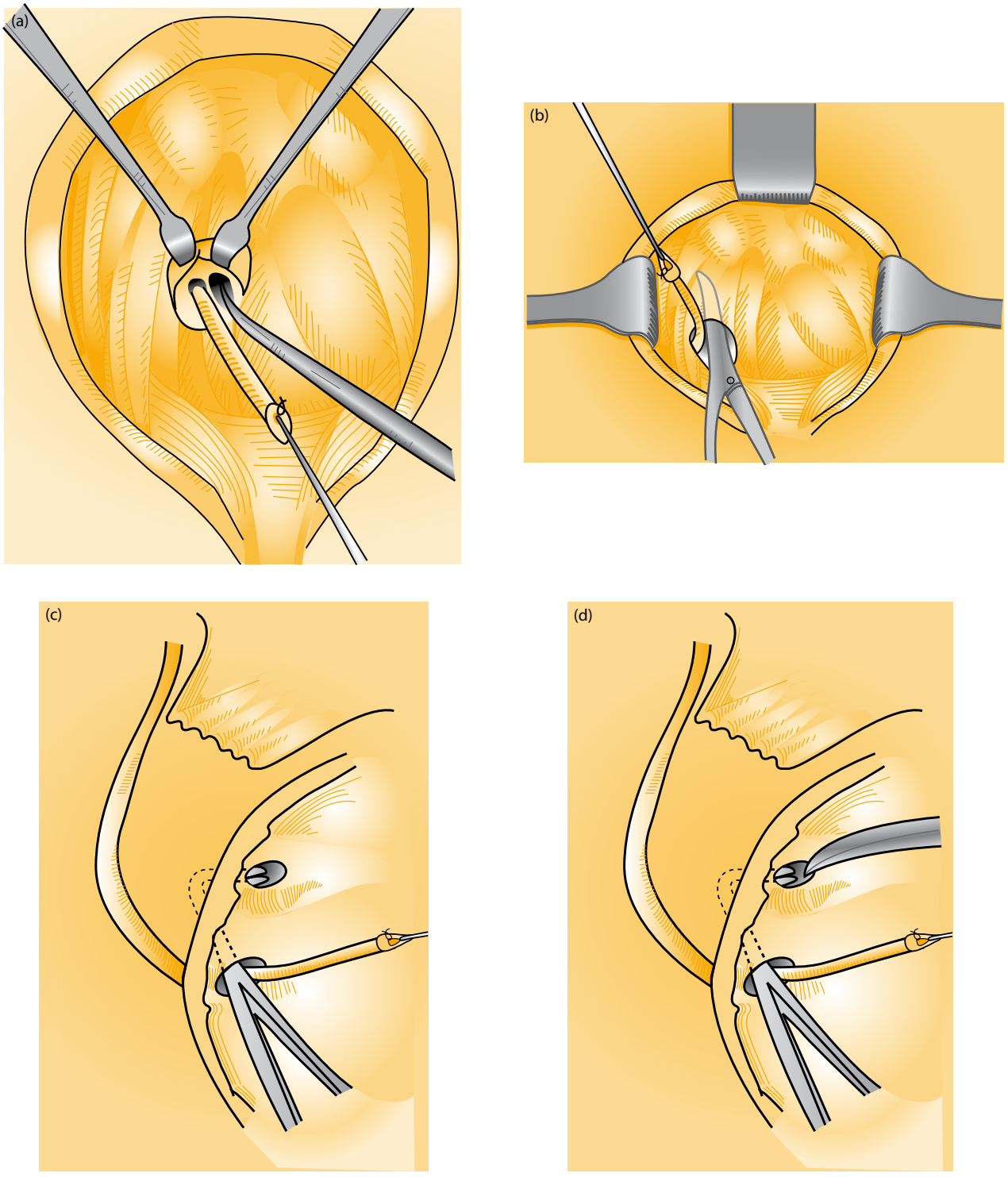
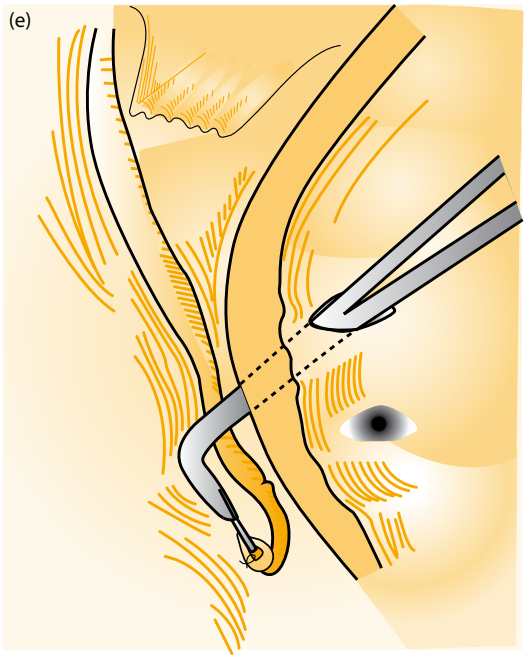
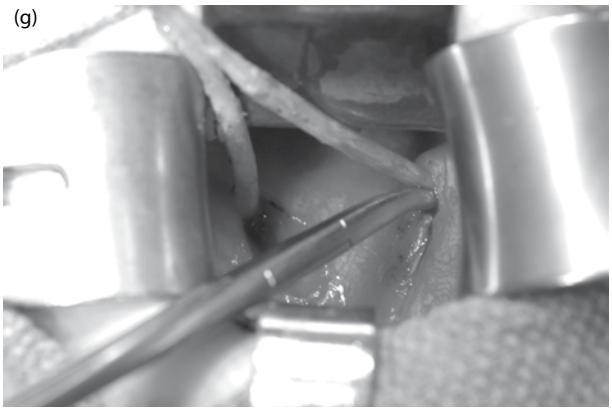
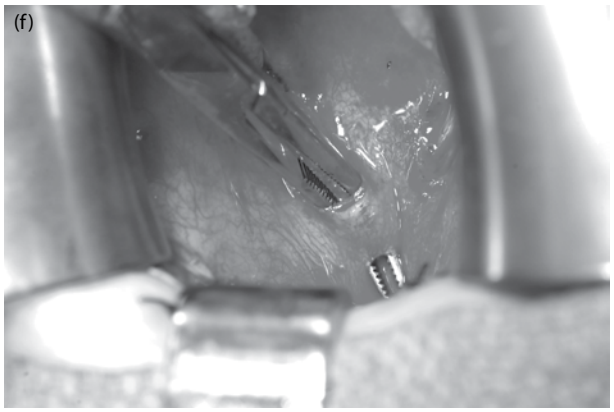
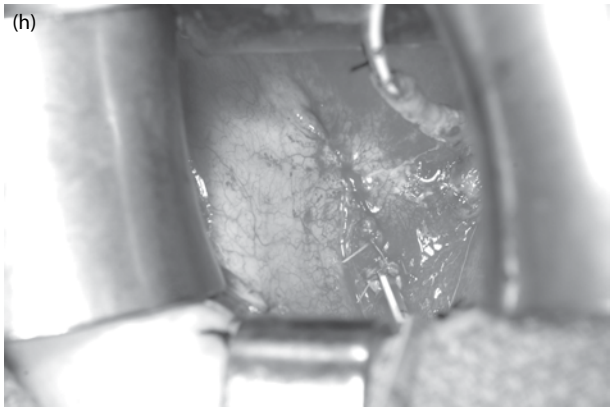


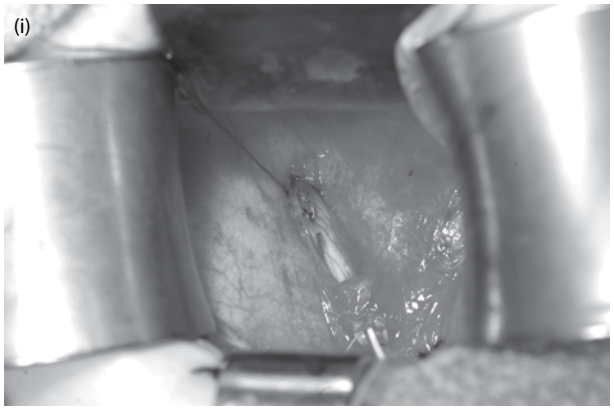
FIGURE 44.7 (a) Following adequate ureteral mobilization, the peritoneum and other structures (vas deferens or vagina) are displaced under direct vision. The posterior aspect of the bladder may be opened to allow for better visualization during this dissection. (b) Once the peritoneum is swept away, a right angle clamp is passed from the original hiatus, indenting a region superior and medial to the native hiatus. The electrocautery device incises the bladder tissue indented by the clamp. (c) The new hiatus is opened widely with the tip of the right angle clamp to allow for accommodation of the ureter. (d) A second right angle clamp is passed from the new hiatus down through the original hiatus. (*Continued*)











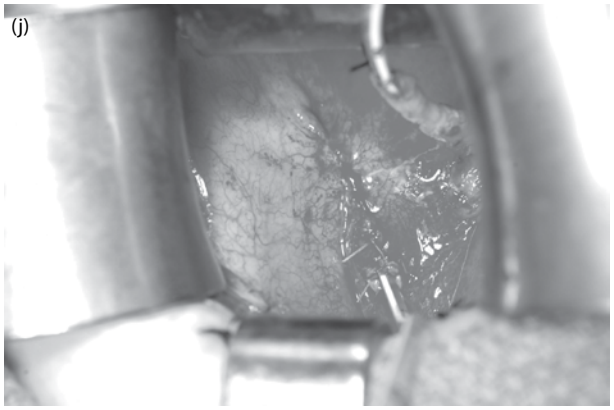


FIGURE 44.7 (Continued) (e) The ureter is then grasped by the second clamp after amputating the distal aspect of the feeding tube. (f) A new submucosal tunnel has been created distally, as illustrated by the right-angle clamp. (g) The detrusor muscle has now been closed with fine absorbable suture and will serve as a muscular backing for the ureter. The tip of a Schnidt clamp has been placed next to the ureter to ensure the new muscular hiatus is not overly tight. (h) The right ureter is laid down into the new submucosal tunnel. (i) The ureter is anastomosed to the bladder using an interrupted vicryl suture. (j) The mucosal defect has been closed over the right ureter using a fine absorbable suture in a running fashion. (Photos in panels f–j courtesy of Anne Raynor, Vanderbilt University Medical Center, Nashville, Tennessee.)

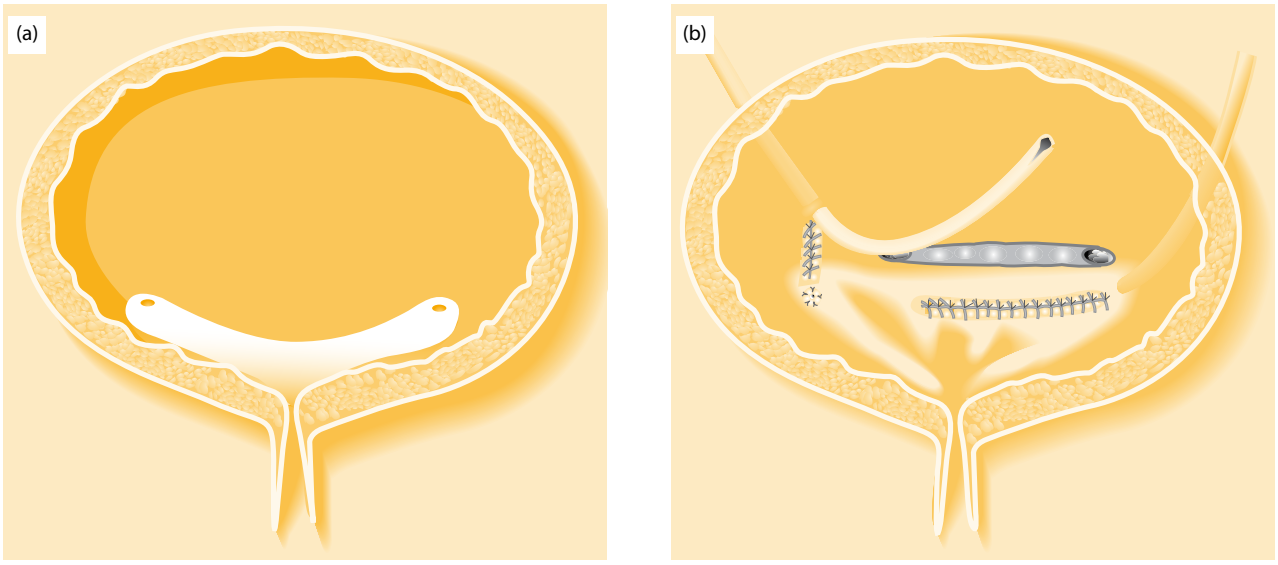


FIGURE 44.8 (a) Laterally displaced, refluxing ureteral orifices with an adequate posterior bladder wall for cross-trigonal reimplantation. (b) The left ureter was reimplanted using this technique. The native right ureteral orifice becomes the new left orifice after reimplant. The right ureteral muscular hiatus is incised superiorly to shift the ureter in a cephalad fashion, allowing a smooth tunnel for cross-trigonal reimplantation.

hiatus. Visual inspection of the anatomy of the trigone and posterior bladder wall aids the surgeon in deciding how to orient the ureters in regards to superior and inferior location. At times, proper positioning of the submucosal tunnels dictates carefully incising the posterior bladder wall following peritoneal displacement in a superolateral fashion (Figure 44.8b). This leads to a cephalad shift of the ureter at the muscular hiatus, and allows for a smoother course across the posterior bladder wall for the superiormost ureter. Additionally, a lateral, muscular incision may be performed to recess the ureter laterally and can be used to increase the tunnel length in small bladders. Following ureteral reimplantation, the bladder is closed in two layers using a 3-0 chromic suture.

Glenn–Anderson Repair

In 1967, Glenn and Anderson refined and popularized the intravesical ureteral advancement procedure that had been reported by several other authors.[15,21,22] Patients in whom this technique is used are selected based on the location of their refluxing ureteral orifices (Figure 44.9a). Those patients with laterally displaced ureters and a sufficient posterior bladder wall are good candidates for this procedure.

Ureteral dissection is performed in a fashion as described previously. If the muscular hiatus is gaping, the muscle edges are approximated with a buried 3-0 chromic suture, allowing for an adequate, smooth entrance for the ureter. Following ureteral mobilization, a mucosal tunnel or mucosal flaps are developed from the original mucosal hiatus and extended in a caudal fashion to a point marked superior to the bladder neck. Once the tunnel or flaps are created, the ureter is either transferred through the tunnel or placed in the mucosal trough. The ureter is then secured distally to the newly created mucosal hiatus in a manner similar to that of the Politano–Leadbetter technique. The mucosal hiatus is then matured circumferentially with interrupted absorbable sutures, or the mucosal trough is closed with a running fine absorbable suture (Figure 44.9b). The bladder is then closed in a fashion similar to that of the other repairs.

Gil-Vernet Repair

A simple advancement technique for those patients with lateral ectopia and a widened "megatrigone" was described by Gil-Vernet in 1984.[23] Exposure of the ureters is similar to that in other open procedures; however, minimal ureteral dissection is needed. A traction suture is placed at the medial aspect of the ureteral orifice, and adequate mobility of the distal ureter and intrinsic muscular fibers of the terminal ureter is demonstrated by the ability of the ureter to be pulled toward the midline (Figure 44.10a and b).

If mobility of the distal ureter is found to be adequate, a transverse incision is made through the mucosa across the superior aspect of the trigone between the ureteral orifices. The mucosa is then elevated off the bladder wall muscle. The classic description by Gil-Vernet uses a single 3-0 nylon or proline suture placed in a mattress fashion at the base of each ureter, encompassing the periureteral sheath and muscle. This suture advances the ureters toward the midline, increasing their intramural length. The permanent suture is then buried by approximating the bladder muscle with 3-0 chromic sutures. The mucosa is then closed vertically with interrupted, fine absorbable sutures (Figure 44.10c). A modification of this technique using absorbable suture for the medial advancement has been described, and that is our practice at VCH.[24] The bladder and the overlying incision are then closed in a routine fashion.

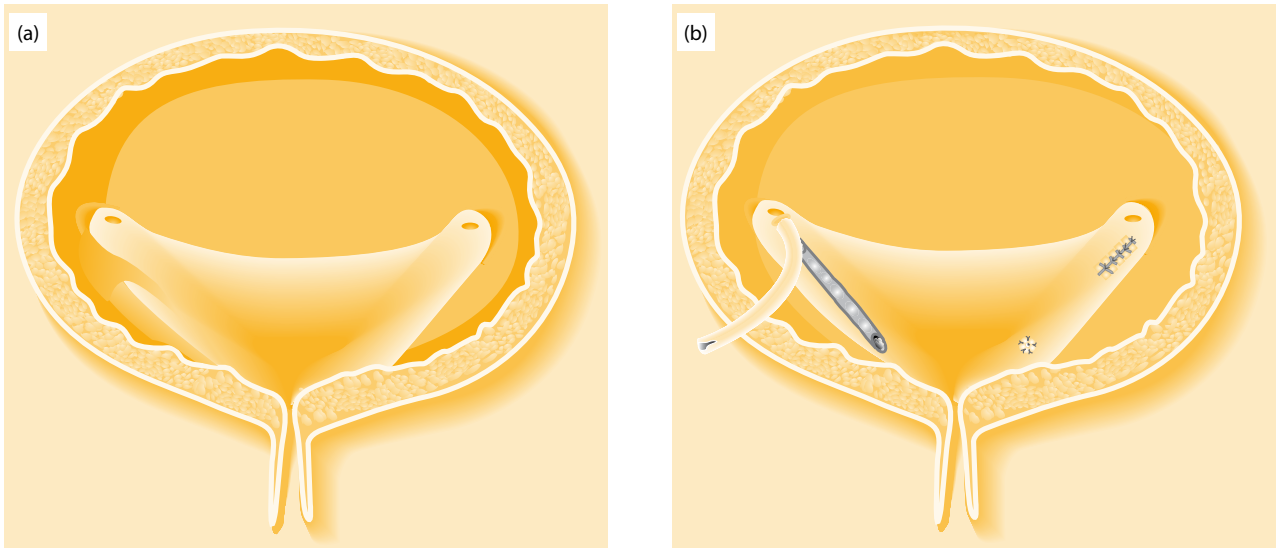


FIGURE 44.9 (a) Lateral and cephalad ureteral orifices that are ideal for the Glenn–Anderson advancement technique. (b) The ureters are advanced to an area superior to the bladder neck with an adequate submucosal tunnel.

EXTRAVESICAL TECHNIQUES

Lich–Gregoir Repair

An extravesical approach to the correction of VUR was almost simultaneously described in the United States and in Europe by Lich and colleagues and Gregoir and Van Regemorter in the early 1960s.[13,14] This technique, commonly referred to as Lich–Gregoir, is similar to previous methods published by others around the turn of the twentieth century.[4,25] Despite its popularity in Europe, American surgeons were less enthused following Hendren's disappointing initial results using a modification of this repair.[26] Subsequent studies with minor modifications have found this technique to be both durable and reliable.[27,28]

Because the bladder is not opened during the repair, cystoscopy is performed prior to opening to rule out any bladder abnormalities. Once cystoscopy is complete, a Foley catheter is placed and clamped, and the bladder is left moderately full. Bladder exposure is obtained in a fashion similar to that for the intravesical repairs. The bladder volume is then emptied, and the bladder is retracted medially to expose the refluxing ureter. The peritoneum is reflected superiorly away from the posterior bladder wall, and the obliterated hypogastric artery is identified and ligated. The ureter is then found, mobilized, and freed of attachments distally to the posterior aspect of the bladder (Figure 44.11a). A network of small vessels typically congregates near the ureterovesical junction, and they need to be divided carefully with the electrocautery.

Following ureteral mobilization, the serosal and muscular layers of the detrusor are incised superiorly 4–5 cm to create a trough for the ureter. The bulging bladder mucosa is seen following muscular division and ensures adequate mucosal exposure. Distension of the bladder during this

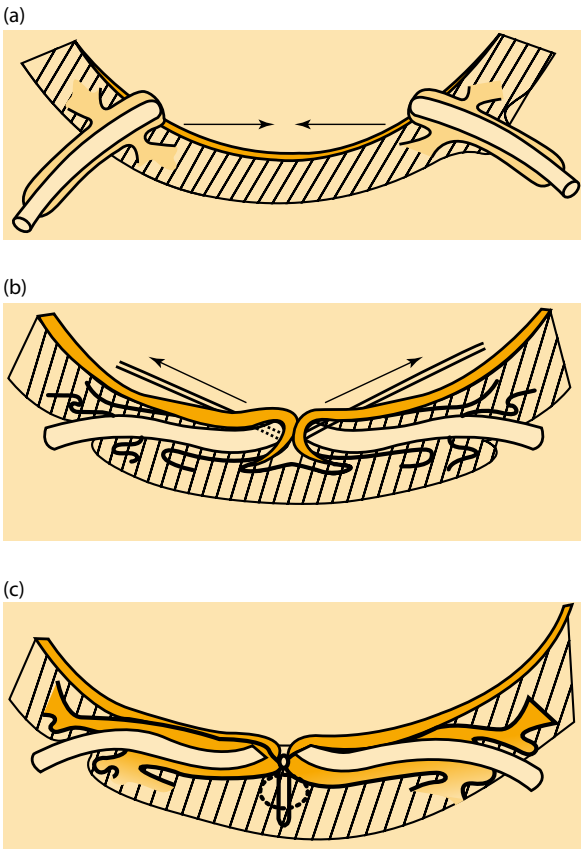


FIGURE 44.10 (a) The Gil-Vernet technique of advancing mobile ureters across the trigone. (b) Traction sutures are placed at the medial aspect of the ureteral orifices to test mobility. (c) Mattress sutures advance the ureters towards the midline, increasing their submucosal tunnel length. (Modified from Gil-Vernet *JM. J Urol* 1984;131:456–8.)

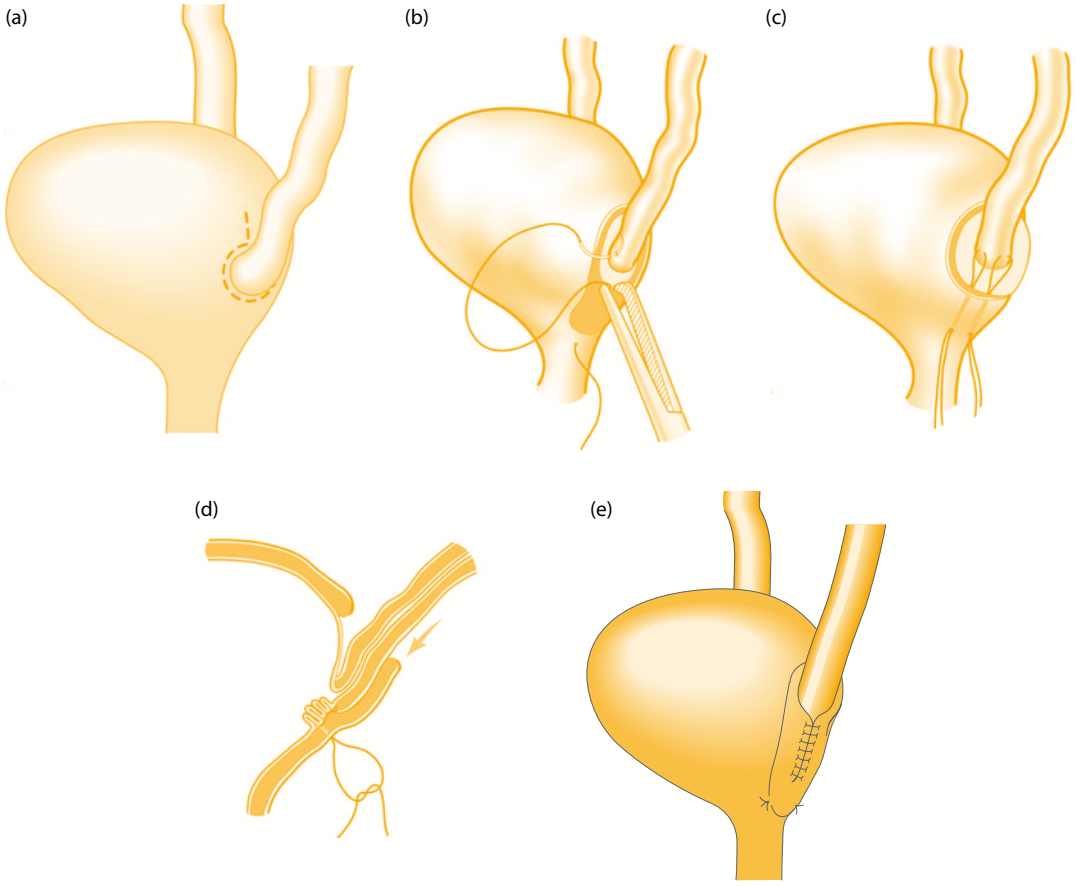


FIGURE 44.11 (a) The extravesical approach begins with ureteral mobilization followed by detrusorrhaphy. (b) After mobilization of the mucosa off the bladder muscle, two or three vest sutures are placed in an appropriate fashion. (c) Tying of the sutures advances the ureter down toward the inferior aspect of the trough. (d) A sagittal view following ureteral advancement. (e) The detrusor is loosely closed over the ureter once secured in the trough.

step makes this dissection easier. Mucosal rents made during this step are closed with fine absorbable suture. The muscular division continues in a caudal direction 1–2 cm past the ureterovesical junction. The ureterovesical junction is freed circumferentially. Mobility of the ureterovesical junction is needed for ureteral advancement. Two to three 4-0 chromic "vest-type" sutures are placed through the bladder wall and ureter to advance and anchor the ureter to the distal aspect of the trough (Figure 44.11b–d). The ureter is then placed in the trough, and the detrusor is closed over it with interrupted 3-0 chromic sutures (Figure 44.11e). Approximation of the muscle edges proximally should be loose, allowing for the tip of a Schnidt clamp at the muscular hiatus. While no perivesical drain is typically used, an indwelling Foley is left overnight and removed on postoperative day 1. If bilateral extravesical reimplants are performed, a voiding trial is initiated prior to discharge because of the risk of transient postoperative bladder retention. Additionally, several centers have reported successful results using the Lich–Gregoir technique for unilateral reimplantation, but approached via a small, 2 cm hernia-type inguinal incision instead of the traditional Pfannenstiel incision.[29–31]

POSTOPERATIVE EVALUATION

The majority of children following simple ureteroneocystostomy are managed without indwelling urethral catheterization or perivesical drainage at VCH. Surgical repair of VUR via a catheterless ureteroneocystostomy at our institution was found to reduce hospital stay when compared with those patients undergoing ureteral reimplantation with a urethral catheter, without increasing complication rates.[32] Most patients are discharged on postoperative day 1, once the child demonstrates adequate po intake.

Standard postsurgical management includes a renal ultrasound at the first postoperative visit at 1 month to assess for the presence of hydronephrosis. Mild, transient hydronephrosis is commonly seen and resolves within the first several postoperative months. Management of persistent severe hydronephrosis will be discussed later in the chapter.

At our institution, voiding and stooling habits are verbally reviewed during all postoperative clinic visits and validated voiding dysfunction questionnaires are administered at every visit.[33] Postoperative bladder–bowel dysfunction is identified and treated aggressively with

educational reinforcement and medications, including laxatives and anticholinergics, when needed. Suppressive antibiotic therapy is continued for 3–6 months following surgery. The child's preventative antibiotics are discontinued on an individual basis. Factors considered in the cessation of antimicrobial therapy include the demonstration of good elimination habits, a consistent UTI-free state, and evidence of resolved hydronephrosis. Routine VCUG in patients undergoing simple ureteroneocystostomy is not performed at our institution, and this approach has been supported by others.[34,35] Following the early postoperative clinic visits, annual or semiannual appointments are made to follow the child's voiding history and check the patient's blood pressure, urine (with a urinalysis), and kidneys with ultrasonography. Later in adult life, periodic evaluation should continue as indicated.

RESULTS

The open surgical treatment of VUR has a long record of impressive correction rates following surgery. Initial and follow-up series of accepted surgical methods have success rates of 94%–99%. The 2010 American Urologic Association (AUA) Guidelines for the Management and Screening of Primary VUR in children found a resolution rate of 98.1 per 100 children undergoing open ureteral reimplantation.[36] In the 1997 AUA guidelines on this topic, reimplanted ureters with grade I–IV VUR had surgical correction rates of 98%–99% independent of technique, and these findings hold true at VCH.[37] However, patients with grade V VUR were found to have a persistent but lower grade of VUR 19% of the time following surgery.[38] Rates of febrile UTI are low following open ureteral reimplantation as well. In the 2010 guidelines, the rate of febrile UTI after surgical therapy, either open reimplant or endoscopic injection, was reported to be 4.9 per 100 children treated. Additionally, the number of postoperative UTIs correlated with the number of preoperative UTIs.[36] Some authors have suggested that patients undergoing open ureteral reimplantation may be at increased risk of febrile UTI following surgery compared with endoscopic injection.[39] At our institution, febrile UTI occurred in 4.6% of patients following open surgery.[40] With improvements in instrumentation and suture material, modifications of techniques, proper performance, and appropriate selection of patients, success nears 99% in those patients undergoing simple ureteral reimplantation with low- to moderate-grade reflux.

COMPLICATIONS

Ureteral Obstruction

Postoperative complications are rare following ureteroneocystostomy. Hydronephrosis is not unusual in the early recovery period and often correlates with the degree of hydronephrosis present prior to surgery. Recent data report the incidence of de novo postoperative hydronephrosis to be 12%. Hydronephrosis resolved in 71% of these patients over a period of 1.3 years.[41] Similarly, in our series of patients who underwent ureteral reimplantation surgery, 8% of patients had grade I hydronephrosis, which resolved over a period of several months.[34] Severe, persistent hydronephrosis is uncommon and likely is related to ureteral obstruction. Fortunately, ureteral obstruction is rare, with an occurrence rate between 0.1% and 1%.[34,35,41,42] In 28 articles reviewed for the 2010 AUA guidelines, ureteral obstruction occurred at a rate of 0.4 per 100 children.[36] Fortunately, the few patients with ureteral obstruction typically present with clinical signs and symptoms that distinguish them from patients with nonobstructive hydronephrosis.[41,43,44] In cases of ureteral obstruction, initial management includes the placement of a percutaneous nephrostomy tube or indwelling stent in hopes that the obstruction is transient and will resolve over time. In patients with persistent ureteral obstruction, a repeat ureteral reimplant is required. This procedure may necessitate significantly more ureteral mobilization than the initial surgery, requiring both an intravesical and extravesical approach. A viable ureter is then found and the distal fibrotic ureter is discarded. A psoas hitch or Boari flap may be needed if a significant length of distal ureter is lost. In rare instances, a transureteroureterostomy or ileal ureter is required for reconstruction.

Persistent Reflux

Persistent reflux following ureteroneocystostomy is rare. The success rate as noted previously exceeds 98% in those with nondilating VUR. Poor selection of patients for specific operative techniques may have led to early reports of persistent reflux following surgery using specific methods.[26] The creation of an adequate submucosal tunnel in children with severe, dilating VUR is challenging. Ureteral tapering is often required, which increases the complexity of the surgery and risk for postoperative morbidity and is discussed in detail in Chapter 36. Fortunately, in most patients with persistent VUR, their reflux is downgraded substantially following surgery and may resolve with growth and good voiding mechanics. One unusual cause of persistent VUR is the development of a ureterovesical fistula postoperatively. This complication does not typically resolve with expectant management. If problematic, surgical correction is indicated.

New Contralateral Reflux

The development of new contralateral VUR following unilateral ureteral reimplantation is uncommon. Occurrence rates vary from 1% to 18% and were reported to be 9.6 per 100 children in the 2010 AUA guidelines.[36,45,46] Possible factors associated with de novo contralateral VUR include a prior history of resolved contralateral reflux, correction of grade V VUR, or VUR into a duplicated system.[45,47] Contralateral VUR is usually low grade, causes no sequelae, and resolves within 1–2 years if the child adheres to a good voiding regimen. The need for surgical correction of new-onset, contralateral VUR following surgery is a rare event.

CONCLUSIONS

The paradigm of treatment for VUR continues to develop as the aggressiveness of evaluating children with UTI evolves. Irrespective of the manner in which children are ultimately found to harbor VUR, the open surgical repair for the correction of VUR remains both a safe and effective management option. Classically described methods, such as the Politano–Leadbetter technique, are successful, durable repairs and continue to be used today. Whereas laparoscopic and endourologic techniques are being performed in greater numbers, the ease and success of the open surgical repair is the standard by which all other repairs continue to be judged.

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CHAPTER 45

Minimally Invasive Approaches to Correct Primary Vesicoureteral Reflux

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INTRODUCTION

There are many controversies among physicians regarding the management and indications for surgical repair of vesicoureteral reflux. However, currently, and probably for many years to come, good medical practice still has a place for antireflux surgeries. As in many other surgical approaches, minimally invasive modalities are gradually being introduced to decrease morbidity and pain, shorten hospitalization, speed up recovery, and provide improved cosmetic results. As the indications for surgical interventions are discussed elsewhere in this book, our aim in this chapter is simply to shed a light on the available minimally invasive options and their history, techniques, and results.

Generally speaking, a new minimally invasive technique must achieve the main surgical principles of traditional surgery. In the case of antireflux surgery, the aim should be to achieve adequate detrusor muscle backing for the intramural ureter, as achieved by open surgery, while elongating the submucosal tunnel, and providing sufficient ureteral mobilization while preserving adequate blood supply.

Unlike minimally invasive options for other urological surgeries, laparoscopic reimplantation techniques have not gained popularity for several possible reasons:

- The high success rate of traditional surgeries, about 95%–98%,[1] and relative ease and familiarity of open procedure, as opposed to the demanding learning curve required for minimally invasive techniques.
- Open techniques can be done through a small incision, usually a Pfannenstiel, with already fast recovery and cosmetic results. Additionally, the hospital length of stay for open surgery is already very short, on average less than 24 hours.
- There exists another minimal intervention, in the form of endoscopic bulking material injection, which is an alternative option, the indications and results of which are discussed elsewhere in this book.
- Compared with ablative surgery, reconstructive laparoscopic surgery is more technically demanding, especially in children, as the working space available for dissection and suturing is smaller.

This chapter discusses five options, namely, percutaneous transvesical trigonoplasty, extravesical (laparoscopic and robot-assisted) ureteral reimplantation, and intravesical (laparoscopic and robot-assisted) ureteral reimplantation.

PERCUTANEOUS TRANSVESICAL TRIGONOPLASTY

This technique was first described simultaneously in 1996 by Okamura and Cartwright and is included mostly for historical perspective, as it was among the first attempts at performing a reconstructive procedure for vesicoureteral reflux using endoscopic techniques.[2,3] This procedure is an attempt at reflux correction using the principles of the Gil-Vernet technique, a method by which the ureters are advanced into the bladder, thus increasing the length of the intravesical portion of the ureters without formally mobilizing them. Although Okamura reported 100% success in the initial 6 cases,[2] a larger series by Cartwright involving attempted procedures on 22 children (32 ureters) had a success rate of 62.5%.[3] Gatti reported on the long-term outcomes of this procedure and showed that the reflux often recurred and that the long-term success rate was 47%.[4] There is at present no role for endoscopic trigonoplasty in the correction of reflux, but these authors are to be commended for their attempts at innovation.

LAPAROSCOPIC EXTRAVESICAL REIMPLANT

The first reported cases of laparoscopic vesicoureteroplasty in humans were performed by Ehrlich et al. in 1993 and Janetschek in 1995.[5,6] Interestingly, the latter, in his conclusion, described it as a complicated procedure offering no advantage over conventional surgery. However, since then, several groups have adopted the technique and reported very good results, comparable to, if not equal to, open surgery.[7,8]

Surgical Technique

- As initially described: Cystoscopy is performed first to assess the bladder wall, the ureteric orifice, and the available posterior wall length for creation of the tunnel. An open-ended 3 or 5 Fr catheter may be inserted in the ureter at this stage, to help identify and protect the ureter during its dissection. This catheter is tied to a Foley outside the urethral meatus, and both should be accessible within the operative field. Later reports found the ureteral stenting unnecessary,[7,8] but either way, a Foley catheter should be placed in the operative field. The catheter should be accessible to control the bladder filling and emptying, which plays a crucial role during dissection of the ureter and creation of the extravesical tunnel.
- The patient is placed in the Trendelenburg position, with legs spread apart and arms tucked to the side. The monitors are placed at the foot of the bed. The surgeon and assistant stand on the contralateral side of the ureter they are reimplanting.
- Port placement: In the original description of the procedure by Ehrlich et al., the umbilical trocar (11.5 mm) is inserted first and used for the camera. Two 10 mm working trocars are inserted in each lower quadrant in the midclavicular line, and an additional 5 mm port is inserted on the contralateral side, 1 inch above the other trocar. More recently, there has been an inclination toward using smaller and fewer trocars. A common practice is to place the three lower ports along the line of a Pfannenstiel incision (Figure 45.1).[7,8] Tsai et al. reported using three 3.5 mm ports, one at the umbilicus for the 3 mm camera, and the other two for 3 mm instruments.[9]
- The next step is exposure of the ureter. It may be identified at the pelvic brim and the peritoneum incised transversely over it, or alternatively, the peritoneum is incised adjacent to the bladder. That incision is just caudal to the vas in males, reflecting it cephalad, or between the broad ligament and the bladder base in females. A vessel loop can be passed through the midline lower port, passed under the ureter, and used for traction. The bladder should be half full at this stage. The ureter is dissected cranially and caudally, freeing it from surrounding structures using blunt dissection and minimal cauterization. Care must be taken not to skeletonize the ureter to preserve its blood supply. There is usually no need to dissect distal to the ureterovesical junction (Figure 45.2).
- A line is demarcated starting at the site of the original ureterovesical junction and directed cephalad, marking the site of the tunnel. A traction suture is placed distally using a Keith needle, or alternatively, two suspension sutures are placed percutaneously with the aid of a fascial closure device, on either side of the apex of the proposed tunnel. Another holding suture may be passed through the anterior abdominal wall and then through the proximal end of the tunnel site to provide more traction if needed.
- The seromuscular layer is then incised carefully, using electrocautery and sharp scissors, without injuring the bladder mucosa, to create a trough (Figure 45.3). The degree of bladder filling and the bulge of mucosa can be adjusted at this point using the urethral catheter in the field. If the mucosa is accidentally punctured, it should be repaired with a figure eight stitch of fine absorbable suture. There is no need to undermine the mucosal edges of the tunnel. An advancing suture, which is taken at this point in open surgery from the distal end of the ureterovesical junction, fixing it to the most distal point of the trough, is not applicable in most laparoscopic cases, as the distal attachment of the ureter to the bladder wall is left intact. An inverted-Y detrusorotomy is not routinely performed, and required only if closure of the distal tunnel is under tension.
- The distal ureter is laid in that tunnel and the edges closed over it with interrupted absorbable sutures, taking care to avoid suturing and obstructing the ureter.
- After closure of the tunnel, the traction sutures are released and the bladder is filled and cycled to exclude leaks and ureteral kinks.

Results

The importance of proper surgical techniques cannot be overemphasized for this procedure. One of the concerns when performing extravesical ureteral reimplantation is the denervation of the bladder, which can lead to transient

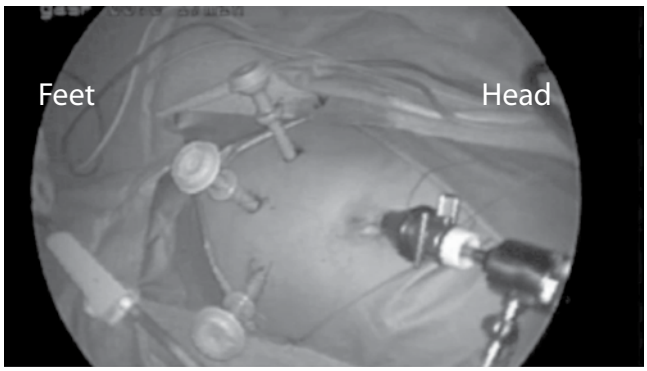

FIGURE 45.1 Suggested port positions for laparoscopic extravesical reimplantation. Camera in the umbilicus and three ports along the line of a Pfannenstiel incision. (Courtesy of J.-P. Capolicchio, MD.)

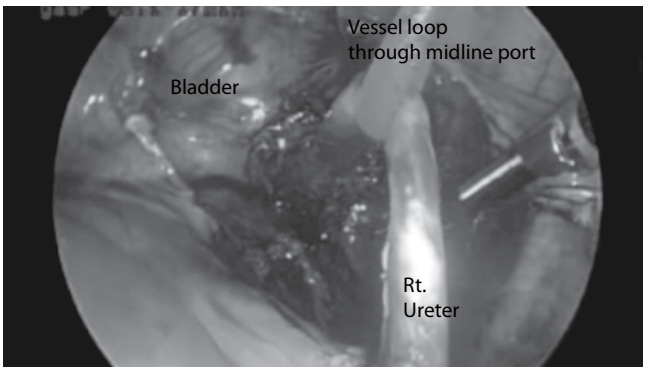

FIGURE 45.2 Exposure of the ureter for extravesical reimplantation, from pelvic brim to the ureterovesical junction. (Courtesy of J.-P. Capolicchio, MD.)

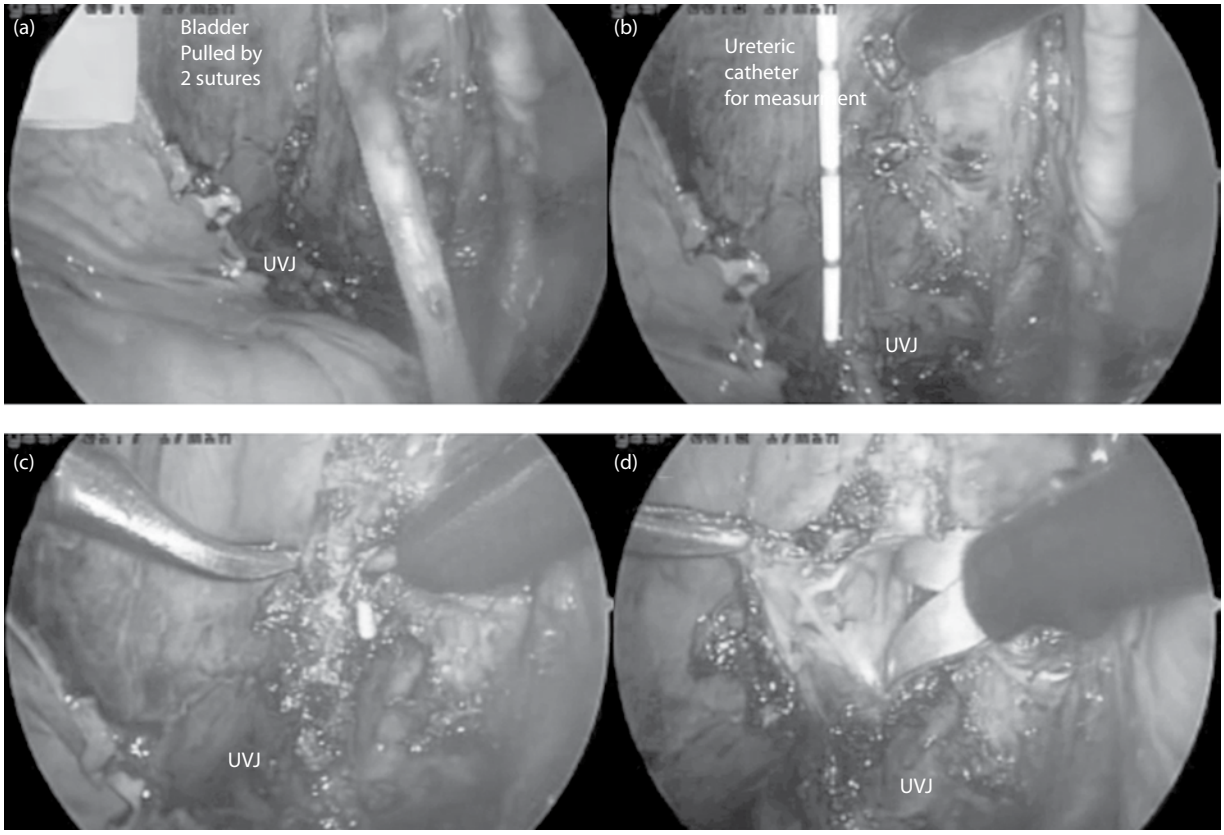

FIGURE 45.3 Steps of tunnel creation for extravesical reimplantation. UVJ, ureterovesical junction. (Courtesy of J.-P. Capolicchio, MD.)

or prolonged urinary retention at the time of catheter removal, especially in bilateral cases. However, according to the more recent literature, this may no longer be as common as it was previously thought to be,[8,9] but if it occurs, it is certainly distressing to the patient, the family, and the surgeon. An important factor to consider while performing this surgery is to minimize dissection and handling of the distal ureter and the lateral bladder wall, aiming for a "nerve-sparing" technique.

Many authors have described the technique with different variations. The results are overall comparable to those of open surgery. In 2000, Lakshmanan and Fung reported on 71 ureters in 47 patients,[7] with resolution of VUR in 100%. However, they reported three complications in the form of distal ureteral necrosis, and that was attributed to prolonged traction on the ureter using a Babcock. In 2006, Riquelme et al. reported their results on 19 patients, of which 18 (95%) were cured and 1 was downgraded.[10] They also reported that they had three mucosal perforations but no significant postoperative leakage. Worth mentioning is that their series included double ureters. In 2008, Capolicchio described his experience with 20 patients over 5 years. As he discussed his results and complications, he showed that their complications, including two cases that were converted to open surgery, were among the first few cases.[8] In the same year, Tsai et al. reported their experience with mini-laparoscopy, and they had excellent results with 11/14 cured and 2 downgraded.[9]

With the improved experience and techniques, urologists have become more willing to apply laparoscopy for more complicated cases, as in megaureters,[11] double ureters, ureteroceles, and even diverticulae.[10,12]

ROBOTIC EXTRAVESICAL REIMPLANT

Robotic surgical techniques have been increasingly accepted and adopted in pediatric urology. The da Vinci® system (Intuitive Surgical, Sunnyvale, California) offers advantages over conventional laparoscopy, including three-dimensional vision and articulating instruments. Additionally, as robotic surgery has become a mainstay in adult urologic surgery, the younger generation of urologists has adopted the robotic technique for reconstructive surgery in favor of standard laparoscopy. One of the main reasons for this shift is the more manageable learning curve with robotics than with traditional laparoscopic surgery. The first reports of robotic ureteral reimplantation were by Peters in 2004,[13] and since that time, there have been multiple additional contributions describing the technique.

Technique

- The steps for robotic reimplantation are similar to those for the transperitoneal extravesical laparoscopic technique, as detailed above. The primary difference is port and camera placement, as the instruments and camera are larger.
- A 12 mm camera port is placed in the umbilicus using the Hasson or Veress needle technique, depending on

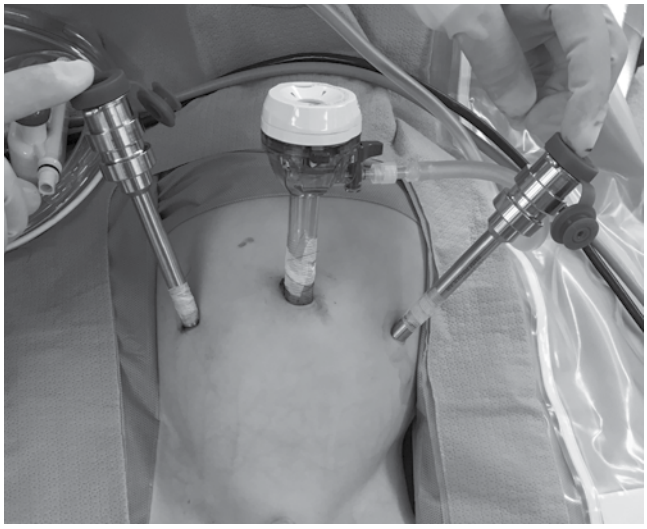

FIGURE 45.4 Port placement for robotic extravesical ureteral reimplant.

surgeon preference. Two 8 mm robotic ports are then placed lateral and slightly inferior to the umbilical port. It is important to ensure adequate distance between the working ports and the camera port as to minimize clashing of the instruments during the procedure. Typically, 8–10 cm (or a hand's width) is adequate (Figure 45.4). Conversely, one could use the 8 mm robotic camera and the 5 mm robotic arms, but this would limit the available robotic instrumentation.

- An assistant port may be utilized if the surgeon desires. This is typically a 10 mm port, although a 5 mm port could be used as well, to accommodate passage of needles or other instruments necessary for the operation. The assistant port is placed on the ipsilateral side of the reimplant and placed midway between the camera and the working port and slightly cephalad, so that the assistant can easily access the port while the robot is docked.
- The position of the robot while docking depends on laterality, patient size, and which da Vinci system is being used. The new da Vinci Xi robot can be docked from a more versatile position. Here we describe positioning for the da Vinci Si robot. All patients are positioned in the supine position. For small children, the robot can be docked directly from the foot of the bed with the patient positioned as far to the foot of the bed as possible. In larger patients, for whom the robot will not reach the ports from the foot of the bed, the robot is docked at a 45° angle from the ipsilateral side of the bed. The robot base should straddle the ipsilateral corner of the base of the operating table to provide optimal positioning. Prior to docking, the patient should be placed in a small degree of Trendelenburg in order to allow for more space in the pelvis, as the bowel will move to the upper abdomen.
- Cystoscopy for evaluation of the bladder wall, ureteral orifice position, or placement of a ureteral catheter is optional, but the technique is the same for nonrobotic laparoscopic extravesical ureteral reimplant. In these authors' experience, ureteral catheter or stent placement during cystoscopy prior to robotic laparoscopic dissection adds rigidity or immobility to the ureter, which makes manipulation of the ureter and placement into the new detrusor tunnel more difficult. Although the presence of a ureteral catheter can be helpful in initial ureteral identification, its advantage is far outweighed by this unwanted technical disadvantage.
- An orogastric or nasogastric tube is placed by anesthesia, and a Foley catheter for intraoperative bladder filling is placed prior to prepping the patient.
- The dissection of the ureter is the same as in the laparoscopic technique described above. Again, a vessel loop or umbilical tape can be used for retraction purposes, and it is critical to ensure that the ureter has been dissected distally to the ureterovesical junction. However, the authors prefer not to use it, given the possibility of ureteral necrosis, associated with aggressive retraction. The extravesical tunnel is then created with electrocautery, and the bladder mucosa is easily seen bulging out in the created tunnel.
- Care should be taken not to violate the bladder mucosa. However, if a hole is created, it can be closed with an absorbable suture, if necessary, to complete the dissection.
- These authors do recommend dissecting the detrusor off of the bladder mucosa laterally on each side of the tunnel when doing this operation robotically, although this is based on surgeon preference.
- A small ruler is passed through the assistant port to measure the tunnel length. Typically, 3–4 cm is an adequate length.
- The ureter is then laid into the tunnel, and absorbable sutures are used to close the detrusor over the ureter. Suture selection is variable, but these authors use 4-0 vicryl sutures.
- The interrupted horizontal mattress technique is used to close the tunnel. A small bite of the ureteral serosa should be taken in the first few stitches to anchor the ureter in place. After the tunnel is completely closed, the traction sutures are removed and the bladder cycled as described above.

Results

Robotic-assisted surgery offers better visualization and articulating instruments, which give it an advantage over pure laparoscopy. Early on in its adoption, robotic extravesical ureteral reimplantation offered promising results for both unilateral and bilateral procedures. Smith et al. reported on 25 cases (33 renal units), with a success rate of 97% and a transient postoperative voiding dysfunction in 3 out of 8 bilateral cases (37.5% of bilateral cases).[14] This did not coincide with the reported results by Casale et al. in 2008 that showed no episodes of urine retention after 41 cases and a success rate of 97.6%.[15] In 2012, the same group (Kasturi et al.) presented their experience with 150 bilateral robotically assisted transperitoneal extravesical ureteral reimplants. They had a 99.3% success rate, and none of their patients developed de novo voiding dysfunction on prolonged follow-up.[16] More recently, however, studies have shown lower success rates and increased complication rates. In 2015, a large multi-institutional study of 61 patients (93 ureters) had only a 72% success rate at mean follow-up of 11.7 months.

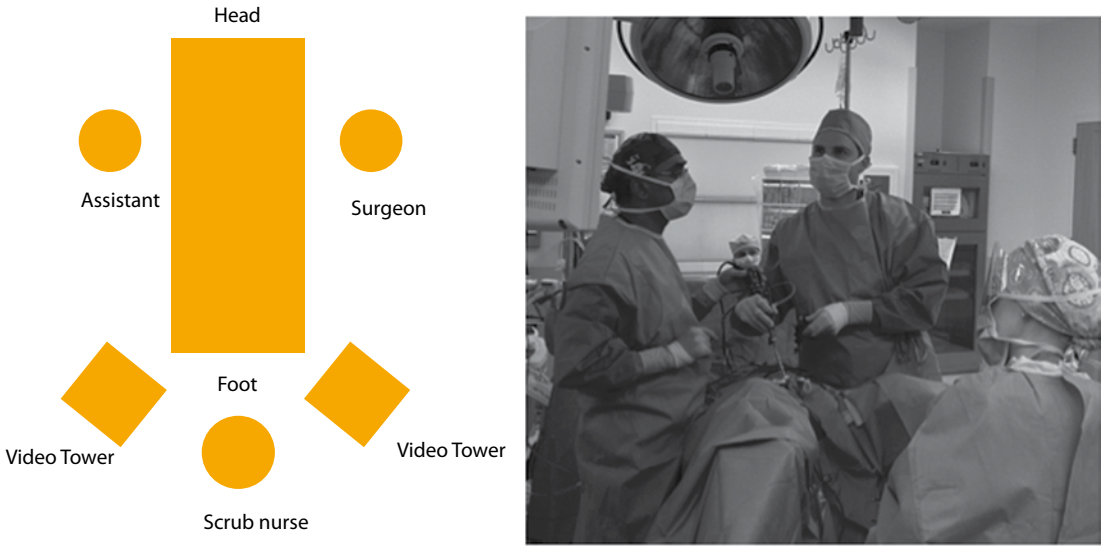

FIGURE 45.5 Position of the surgeon, assistant, nurse, and monitors for vesicoscopic intravesical reimplant. Patient is in the lithotomy position.

In addition to this lower success rate, complications were quite high, with 23% having persistent vesicoureteral reflux, 10% with complications, and 11% requiring reoperation.[17] Subsequently, a large single-institutional study reported similar inferior success rates and found that when stratifying for unilateral and bilateral procedures, there was a significant difference. Unilateral robotic reimplantation had a success rate of 91.5%, while bilateral was only 77.8% successful. This study also found that bilateral procedures had higher complication and reoperation rates than unilateral ureteral reimplantation.[18] Not only has the success and complication rate of robotic reimplant been called into question, but also the cost of the procedure has been criticized, with one study finding that in addition to a higher complication rate of robotic ureteral reimplantation, the median hospital cost was also significantly higher ($p = 0.049$).[19] The emerging literature that critically evaluates the efficacy, safety, and cost of robotic ureteral reimplantation is leading most to implement this technology with caution, particularly when compared with the traditional open surgical alternative.

VESICOSCOPIC INTRAVESICAL REIMPLANT

For open surgery, many centers prefer the Cohen cross-trigonal ureteral reimplantation over the extravesical technique, especially in bilateral cases. That is why the feasibility of this technique laparoscopically was investigated and proven possible in animals,[20] and then by Gill et al. in 2001. He used glycerine to distend the bladder.[21] Yeung et al., in 2005, reported a series of 23 ureteral reimplants in 16 children, using an endoscopic cross-trigonal technique under CO_2 insufflation.[22] Several others have reported their experience and modifications to the technique.[23–26]

Technique

- *Positioning*: The procedure is performed with the child in the low dorsal lithotomy position. Areas prone for pressure sores and neuropraxia, including the back, popliteal fossae, and heels, are adequately padded. The abdomen and perineum are included in a single sterile field, since urethral access is needed for initial cystoscopy, port placement, splinting, and catheterization. The surgeon typically stands on the patient's left side, with the assistant, scrub nurse, and monitors positioned over the patient's legs (Figure 45.5).
- *Cystoscopy and marking the port sites*: After the patient is positioned, CO_2 cystourethroscopy is performed using a 30° lens and a rigid cystoscope. Any urine in the bladder is emptied by suctioning through the irrigation port of the cystoscope. When the bladder is distended adequately with CO_2, the sites for port placement are decided. It is desirable to place the ports as cranially as possible with a distended bladder, without traversing the peritoneum. Apart from the potential for bowel injury, if the port traverses the peritoneum, the subsequent pneumoperitoneum may result in poor visibility and distortion of the bladder. Being overcautious and placing the ports too cephalad may make the dissection extremely challenging, since the working instruments will be perpendicular to the ureteral orifices. If pneumoperitoneum is encountered, it may be decompressed by placing a Veress needle through the umbilicus to vent the carbon dioxide.
- *Anchoring sutures*: The first step is to anchor the bladder to the anterior abdominal wall under cystoscopic guidance. Fixation of the bladder provides adequate resistance to allow ports to be more easily introduced into the otherwise freely mobile bladder. Second, in case of inadvertent extrusion of the port during the procedure, having the bladder fixed to the abdominal wall will prevent distortion of the track due to escape of the CO_2 into the prevesical space and collapse of the bladder. Briefly, a 2-0 PDS

suture, after cutting off the needle, is passed through an 18-gauge spinal needle, well past the needle tip, so that the thread goes through and through and both ends of the suture are outside the needle. The abdominal wall and the bladder are then traversed with the needle, at a site immediately cephalad to the site chosen for port placement. Under cystoscopic guidance, the spinal needle is advanced into the bladder. When the needle is advanced, the suture advances into the bladder along with it. After the tip of the spinal needle enters the bladder, the suture within the needle is further advanced to form a loop, called the pulling loop. This loop is retained in the bladder, and the needle is carefully removed. Through an adjacent puncture, the spinal needle is inserted into the bladder again, and the tip is advanced through the pulling loop. Another 2-0 PDS that will ultimately be anchoring the bladder to the abdominal wall is then inserted through the needle, thus placing it through the loop. Retracting both tails of the pulling loop together out of the bladder pulls the anchoring suture, creating a through-and-through suture that can be tied fixing the bladder to the abdominal wall. Fixation sutures are placed in the midline, as well as the lateral walls of the bladder. Alternately, we have noted that applying traction on the anchoring sutures and securing them to the drapes without tying over the abdominal wall serves the same purpose. Removing this is easy, and there is no suture impression on the abdominal wall.

- *Port placement*: A 5 mm port is placed in the midline for the camera. Two 3 mm working ports are then placed. They must be sufficiently lateral and minimally caudal to the telescopic port to give a comfortable working angle at the depth of the bladder base, for the reconstruction. These ports are placed immediately distal to the fixation sutures in the direction of the bladder neck. For most children, 3 mm laparoscopic instruments that are 20 cm in length are ideal (Figure 45.6).

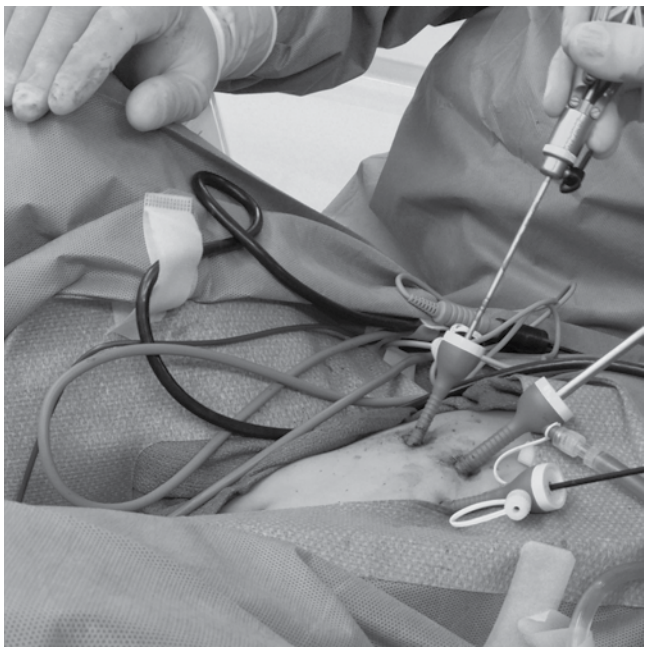

FIGURE 45.6 Suggested port sites for vesicoscopic intravesical reimplant.

- *Ureteral dissection*: Vesicoscopy is performed using a 5 mm 30° lens. The orientation is such that the bladder neck will be located at the twelve o'clock position. Feeding tubes (3.5 Fr) are placed per urethra, passed up each ureter, and fixed with fine suture. Placement of the fixation suture through the tube prior to introducing it transurethrally makes this step easier. Using a hook electrode at a low-power setting begins dissection. Applying gentle traction on the fixation suture away from the line of incision enables precise dissection, retaining a rim of the bladder mucosa with the ureter. Using a combination of sharp and blunt dissection in a manner analogous to open transvesical surgery, the surgeon dissects the ureter off the surrounding detrusor muscle. Extreme care must be used when transecting investing bands of detrusor, and it may be safer to divide these bands sharply as opposed to using cautery. This dissection is rather easy and rapid in children with thin-walled bladders, but it can be quite difficult if a child has a markedly thickened bladder wall. Dissection is continued until enough length is gained to bring the ureter to the contralateral side. The posterior detrusor opening is then closed with an interrupted 4-0 PDS suture. For bilateral repairs, the contralateral ureter may then be mobilized. During the procedure, a suction device is needed to remove not only blood but also urine that may accumulate at the bladder base. Some authors have left a small urethral catheter indwelling to assist with suction, but our preference is to simply use a 3 mm suction–irrigation device through one of the working ports as needed.
- *Tunnel creation*: The tunnel is usually created from the initial hiatus across the contralateral hiatus. Whenever the hiati are located close by and a longer tunnel is required, the mucosa lateral to the contralateral hiatus may be dissected off from the detrusor to increase the tunnel length. With a combination of blunt and sharp dissection, a submucosal tunnel is created. Maryland graspers are used to elevate the mucosa, and fine scissors are used to initiate and develop the plane. The positive pressure within the bladder along with the optics of the 30° lens can assist with visualizing the appropriate plane. After creation of the tunnels, the ureters may be placed in the tunnels and passed to the other side. The feeding tube splint anchored to the ureter often helps in guiding the ureter through the tunnel. The ureters are then fixed in place with an interrupted 5-0 polydioxanone suture. The remaining mucosal openings are then closed with absorbable sutures and the feeding tubes removed.
- *Port closure*: To maintain the pathway through the incision into the bladder, a feeding tube is placed through each port prior to its removal. Under cystoscopic guidance, the sutures to close the port are placed in a manner analogous to that for the initial fixation sutures. After placing the bladder port closure sutures, a Foley catheter is inserted to decompress the bladder and the fixation sutures are removed. This allows the bladder to fall away from the abdominal wall. The bladder port sutures are then carefully tied and the skin incisions subsequently closed. The Foley catheter is typically removed in 36 hours.

Results

Published success rates approach, but are not yet equal to, those of open repair, ranging from 92% to 96%.[22–27] Most of the failures were early in the series, as the surgeon was learning and refining the technique. To date, in these authors' series, 180 children have undergone vesicoscopy, with a mean age of 79 months (16–226 months). Of these, 164 were female and 16 were male. One hundred thirty-four underwent bilateral reimplantation and 46 were unilateral. There were four open conversions. Observed complications early in the series were persistence of reflux, urine leak, ureteral stricture, and port dislodgement with surgical emphysema, although there have been no complications or adverse effects in the last 50 patients treated. The operative time was significantly more than that for open surgery, especially in early cases. It is a technically challenging procedure, but may be justified given the demonstrable reduction in analgesic requirements compared with open surgery.[22,28]

ROBOTIC INTRAVESICAL CROSS-TRIGONAL REIMPLANT

Peters and Woo, in 2005, presented their initial experience trying to combine the benefits of the transvesical approach with the minimal invasiveness of robotic surgery.[29] The drawback at that time was the need for a 12 mm camera port and two 8 mm robotic cannulas. This may be less of an issue with the current and future smaller robotic cameras, ports, and instruments.

The steps after port placement are the same as described above for laparoscopic vesicoscopic cross-trigonal reimplants. The difference lies in the technique of port insertion and port site closure at the end, as the ports are much larger. These authors also noted that the metal of the robotic trocars tends to be very slippery, and it is difficult to keep their position in the skin, even with traction stitches. One technique to help combat this problem is to advance them through a VersaStep™ sheath, which tends to reduce the amount of displacement of the trocar during the procedure.

Results

In their report, Peters et al. tried this technique on six patients, and mild reflux persisted in one of them (83% success rate).[29] In 2011, Marchini et al.[30] published a comparative study in which they had two groups of children that underwent robotic-assisted reimplantation; one group was intravesical (19 patients) and the second extravesical (20 patients). They were compared with a matched cohort of patients that underwent open surgery, 22 intravesically and 17 extravesically. They showed similar success rates in all groups. The robotic-assisted intravesical approach had shorter operative stay, shorter postoperative catheterization, and fewer bladder spasms than the open intravesical group. The difference in bladder spasms was not as pronounced in the extravesical groups. However, both robotic-assisted groups had a significantly longer operative time than the open ones.

CONCLUSION

As surgeons gain experience in laparoscopy and robotic-assisted surgery, we predict that there will be an expanding role for minimally invasive techniques in the correction of reflux. As we have shown, several minimally invasive techniques have been employed, including pure laparoscopy and robotic-assisted laparoscopy, through extravesical and transvesical approaches, which provide valid options with comparable success rates to open surgery.

MULTIMEDIA FILES AVAILABLE ONLINE (www.crcpress.com/cw/Docimo)

VIDEO 45.1 Laparoscopic Extravesical Ureteral Reimplant.

VIDEO 45.2 Laparoscopic Vesicoscopic Reimplant.

VIDEO 45.3 Robotic Ureteral Reimplant.

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CHAPTER 46

Injection Therapy for Vesicoureteral Reflux

Anthony A. Caldamone

INTRODUCTION

Vesicoureteral reflux (VUR), one of the most common urologic abnormalities in children, occurs in 0.4%–1% of the general population and in 30%–50% of those children who present with urinary tract infections (UTIs).[1] When correction of VUR is determined to be necessary, historically ureteral reimplantation by a variety of techniques has been the mainstay of treatment. This approach is justified because surgical correction affords a very high success rate, approaching 99% in experienced hands, and a low complication rate.[2]

The search for a less invasive approach to the correction of reflux, however, dates back to 1981, when Matouschek[3] first described the injection of polytetrafluoroethylene (PTFE) at the ureteral orifice to correct VUR. Reports then followed by McDonald and McDonald.[4] After using PTFE for incontinence, Politano then reported on its use in VUR.[5–8] Puri and O'Donnell brought this clinical concept to the laboratory and demonstrated the successful correction of experimentally produced VUR in a piglet model by the intravesical injection of PTFE.[9] In their classic article in 1986, they reported on the successful endoscopic correction of primary VUR in 103 ureters, achieving a success rate of 75% after a single injection.[10]

This approach earned widespread international acceptance but only sporadic usage in the United States because of the lack of Food and Drug Administration (FDA) approval. It was quite apparent, however, that the potential for revolutionizing the management of children with VUR was real. Although the procedure requires general anesthesia and possible repeat injections, the ease of treatment, lack of open surgery, and minimal hospitalization were extremely attractive in the pediatric population. However, the lack of demonstrated long-term safety and concerns raised in experimental and clinical settings on the potential migration of PTFE particles prohibited its widespread acceptance in the United States. It was quite clear, however, that while the material had its drawbacks, the technique itself was reproducible and reliable. The search was on, therefore, for a substance that would fulfill the following characteristics: ease of injection, maintenance of injected volume, minimal host response, no evidence of distant migration of material particles, maintenance of the injected mound without shifting, and no significant volume loss, longevity of effect, and biocompatibility. The mechanism for the endoscopic correction of VUR involves one or more of the following effects: (1) improved backing of the intramural ureter, (2) fixation of the ureterovesical junction (UVJ) to the trigone by spot welding, or (3) decreased caliber of the distal ureter.

In this chapter, we review the substances that have been used both experimentally and clinically for the endoscopic correction of reflux. In addition to the use of this technique for primary VUR, the applicability of the endoscopic correction technique to other reflux variations is also discussed. Finally, as with any new technology, one must address the issue of whether this new technology changes the indications for surgical correction of VUR.

TECHNIQUE OF ENDOSCOPIC INJECTION

The technique of endoscopic injection for correction of VUR has changed little since it was first described by O'Donnell and Puri.[11] The technique is relatively independent of the material used, although variations in material properties may result in minor modifications in technique. The technique is often referred to as STING, an acronym for subtrigonal injection (Figure 46.1).

Under cystoscopic control, the orifices and bladder mucosa are inspected. Whereas the type of cystoscope is not critical, an offset lens system allows for a straight route for the needle through the scope, which is especially helpful if using a metal needle (Figure 46.2). The degree of bladder filling is critical, as a full bladder may make it more difficult to accurately place the material behind the ureter and still be in the wall of the bladder. Either a rigid metal needle or a malleable needle (most commonly 3.7–4 Fr in size) may be used. A syringe of material is fixed to the needle, and for viscous material like PTFE and silicone, a ratcheted metal syringe holder may be needed. The needle is introduced through a cystoscope using a 0° or 30° lens. Under direct vision, the needle is advanced bevel up and introduced submucosally at the six o'clock position of the UNJ (Figure 46.3). Puri and O'Donnell originally reported piercing the mucosa 2–3 mm distal to the UVJ and advancing the needle 4–5 mm into the lamina propria of the submucosal portion of the ureter. Alternatively, for more gaping orifices, the needle can be placed directly through the mucosa at the UVJ. This can be facilitated by hydrodistention of the ureter, by having irrigation flowing through the cystoscope at the time of the injection, thus dilating the ureteral orifice.[13] The critical step

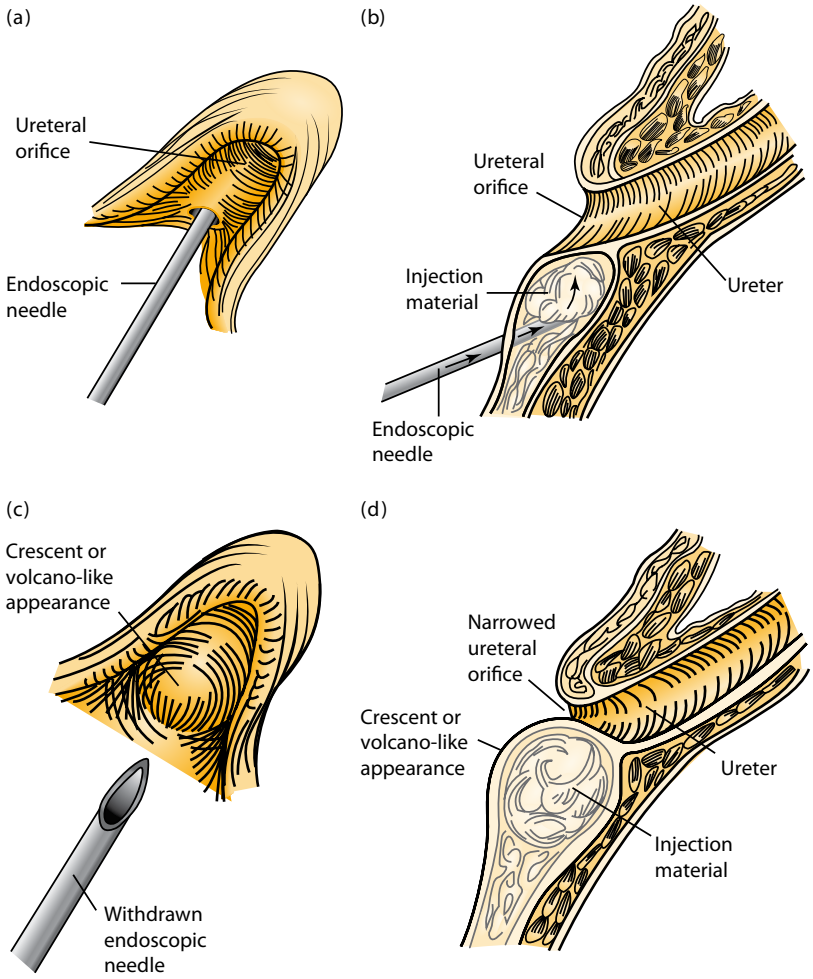

FIGURE 46.1 Standard subureteric injection technique: (a) Needle placed at six o'clock position, bevel upward. (b) Slow injection in subureteric space. (c) Postinjection appearance. (d) Appropriate position of injected material. (Reproduced from Russinko PJ, Tackett LD. *Atlas Urol Clin* 2004;12:55–63. With permission.)

of the procedure is observing the effect from injection of 0.1–0.2 mL. One should carefully assess the positioning of the mound with this minimal initial injection. A "volcanic" bulge should be observed, raising the ureteral meatus onto the dome of the mound. Minor adjustments in the direction of the bevel or the depth of the needle can be made based on the initial 0.1–0.2 mL injection volume. Once the appropriate effect is obtained, more material can be injected to achieve a volcanic mound with a crescent-shaped orifice at the dome (Figure 46.4).

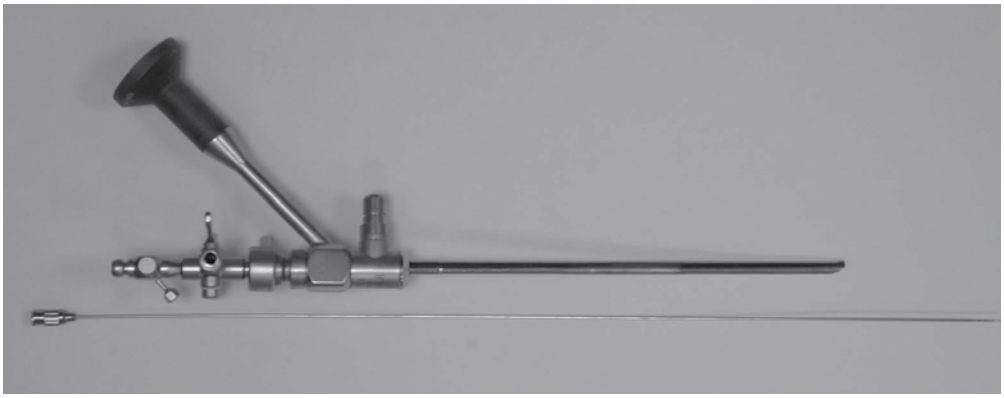

FIGURE 46.2 Offset lens "STINGER" scope, allowing for a straight 4 Fr channel to pass a rigid or flexible needle for injection of material.

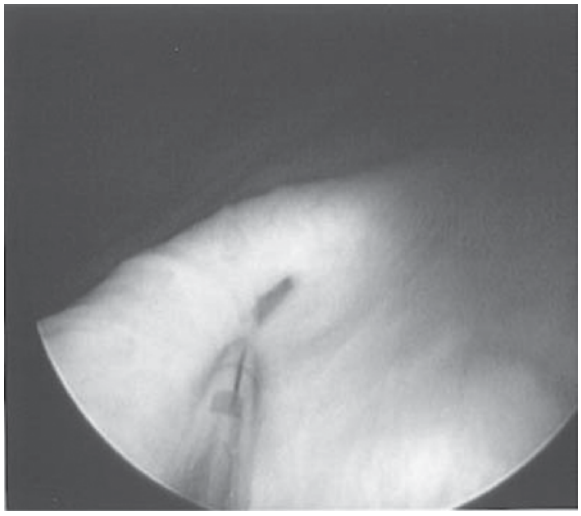

FIGURE 46.3 Needle in six o'clock position at left ureteral orifice subureteric injection.

Depending on the material injected, there is a variable degree of leakage from around the needle or through the needle track once the needle is removed. For PTFE or silicone, the needle should be left in place for 30–60 seconds prior to removal to avoid extrusion. At the conclusion of the injections, the bladder is then drained; viscous 2% lidocaine can be injected into the bladder if desired, prior to cystoscope removal. The patient is discharged from the recovery room on a therapeutic dosage of antibiotics for 3 days, followed by prophylaxis, if indicated, until a postoperative ultrasound and voiding cystourethrogram (VCUG) are done at 3 months. The presence of a well-positioned mound on ultrasound, while reassuring, does not predict successful correction of VUR (Figure 46.5). If reflux is resolved, antibiotic prophylaxis is discontinued and a follow-up ultrasound is done at 1 year.

Postinjection catheter drainage is generally not necessary. Most clinicians recommend antibiotic prophylaxis for 3 months until a follow-up ultrasound and VCUG are performed. If there is persistent VUR, a second endoscopic

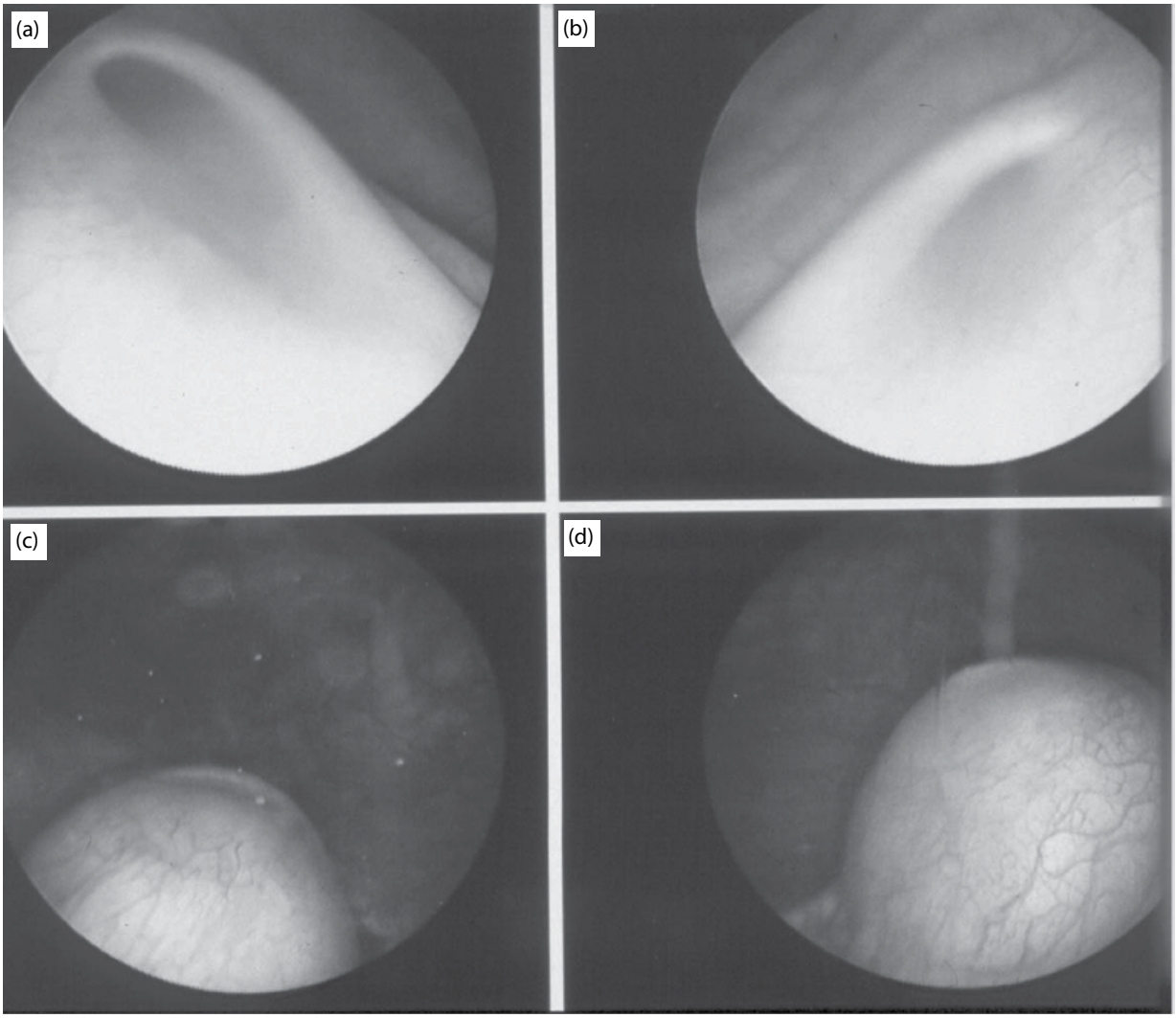

FIGURE 46.4 Endoscopic injection of calcium hydroxylapatite. (a and b) Preinjection appearance of left and right orifices with bladder minimally filled, on top. (c and d) Left and right orifice postinjection, demonstrating a crescent appearance of orifice atop a mound of material.

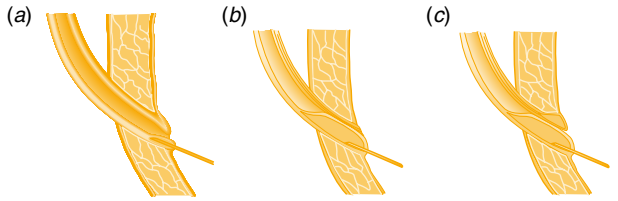

FIGURE 46.5 HIT: Modification of the STING procedure places implant material along the entire subureteral tunnel and leads to greater ureteral wall coaptation. (a) The needle is placed within the ureteral submucosal to the level of the midureteral tunnel. (b) Initial injection causes the floor of the ureteral tunnel to rise up to meet the ceiling of the tunnel. (c) Further injection leads to tracking of implant circumferentially within the ureteral tunnel, resulting in complete coaptation. (From Kirsch AJ et al. *J Urol* 2004;171:2413–16.)

injection can be performed, especially if improvement has been demonstrated after the initial treatment. If failure occurs again, most clinicians would recommend ureteral reimplantation. All studies to date have demonstrated the same high success rate of ureteral reimplantation following endoscopic injection, regardless of the agent used, compared with a primary ureteral reimplantation.[14] It is apparent to most surgeons who have performed endoscopic injection procedures for VUR that, whereas the procedure is relatively straightforward, there are subtle aspects of the technique that are learned over time. Kirsch et al. demonstrated a learning curve over their first 180 cases. The success rate after a single injection for their first 20 patients was 60%, compared with 80% for the last 20 patients in this series.[15]

Kirsch et al. reported on a variation of the classic STING technique in which material is implanted submucosally within the intramural ureter.[13] They referred to this as the hydrodistension technique (HIT). This is accomplished by hydrodistension of the ureteral orifice to allow for injection of the material within the ureteral lumen, rather than injecting in a subureteric position. In a comparative study, they found the success rate with the modified technique to be significantly greater than that with the standard technique, overall 97% versus 79% (Figure 46.5).

Cerwinka et al. have advocated a double HIT for endoscopic injection consisting of two tandem intraluminal ureteric injections (Figure 46.6), one at six o'clock in the midtunnel, which coaps the tunnel. A second injection is made at the more distal aspect of the tunnel close to the ureteral orifice to allow for coaptation of the ureteral meatus. They suggested a classic STING if after the double HIT injection ureteral hydrodistention persists.[16] In a 1-year follow-up of patients in which the double HIT was used, Kalisvaart et al. reported a 93% clinical and radiographic success rate, and raised the question as to the necessity of the postinjection VCUG.[17]

MATERIALS

Many materials have been used over the past 25 years of endoscopic treatment for VUR. Whereas success rates vary little from material to material, other properties—such as ease of injection, particle size and migration, inflammation response, longevity, and biocompatibility—vary greatly (Table 46.1). Materials may be divided into nonautologous and autologous.

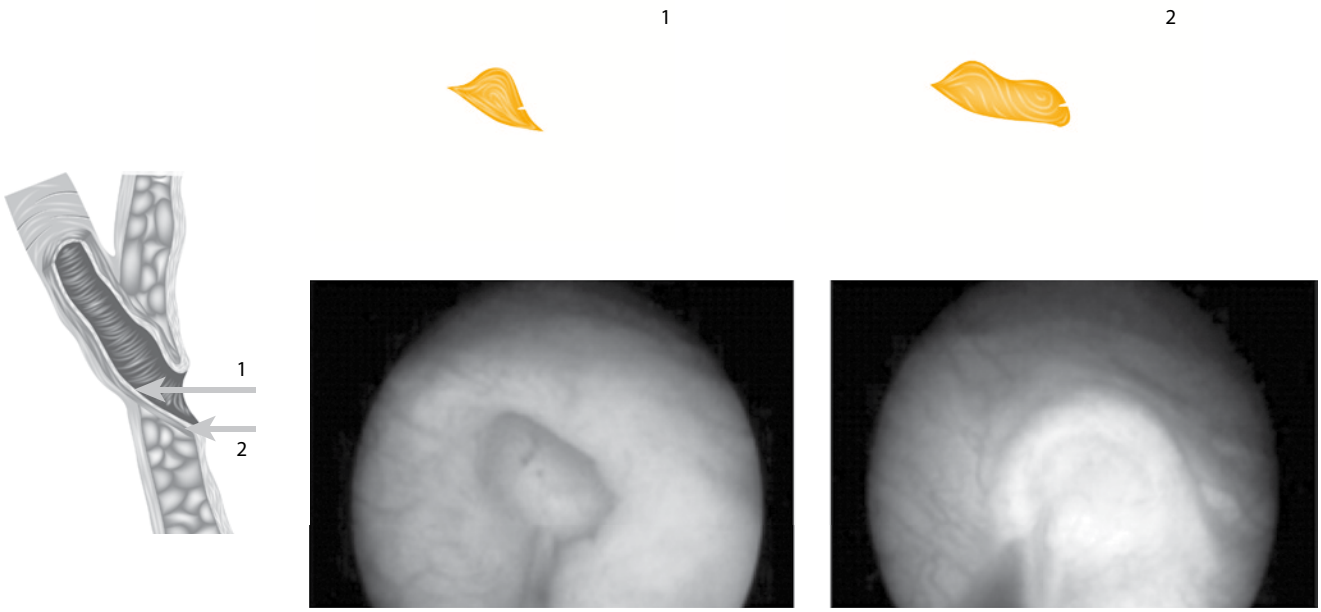

FIGURE 46.6 New double HIT as described by Cerwinka et al. (Courtesy of A. Kirsch.)

TABLE 46.1 Characteristics of available injection materials

Product	Material composition	Particle size (μm)
Teflon, polytef	PTFE particles, which are inert and suspended in glycerin 50% by weight	4–100
Deflux	Dextranomer microspheres cross-linked in 1% sodium hyaluronan solution	80–120
Zyderm, Zyplast, Contigen	Derived from bovine dermis, cross-linked to glutaraldehyde: GAX 35, 35 mg/mL collagen; GAX 65, 65 mg/mL collagen suspended in pH neutral saline	—
Macroplastique	Polydimethylsiloxane (PDMS), a biphasic copolymer polymerized and vulcanized PDMS in polyvinylpyrrolidone hydrogel	35–540; mean maximal diameter, 209 μm
Coaptite	Calcium hydroxylapatite spheres suspended in water and glycerin mixture with cellulose gel former	75–125
Urocol	50% microporous hydroxyapatite ceramic suspended in gel with 4% collagen in glycerin	100–400
Chondrocytes	Auricular chondrocytes suspended in an alginate solution with calcium salt	20×10^6
Fat	Suprapubic adipose tissue obtained by microliposuction	—
Autologous collagen	Extracted from dermis	—Autologous blood
Autologous blood	Extracted from patient	—
Autologous bladder muscle	Extracted from animal	—
Polyacryl polyalcohol copolymer	Synthetic acryl particles	300

Source: Modified from Russinko PJ, Tackett LD. *Atlas Urol Clin* 2004;12:55–63.

Nonautologous Materials

Polytetrafluoroethylene

In 1973, Berg reported a method for the correction of urinary incontinence using an injectable form of PTFE paste.[18] In 1981, Matouschek injected PTFE at the UVJ for the correction of VUR.[3] This was then first studied in an animal model by Puri and O'Donnell,[9] and then in human subjects.[11,19] PTFE, a polymer composed of large molecules formed by chemical combinations of smaller ones into chains, has been used in the manufacture of plastic materials for medical devices for many years, including vascular grafts, cardiac valves and implants, stents, cartilage or bone replacement, sutures, and patches. The paste form of PTFE is a suspension of inert PTFE particles in a glycerin carrier. The glycerin, which represents 50% of the weight, is absorbed by the tissues after injection. The size of the particles ranges from 4 to 100 μm, with approximately 90% <40 μm. Because of its high viscosity, PTFE requires a ratcheted syringe mechanism for injection. Upon injection, a foreign body giant cell reaction occurs with the infiltration of histiocytes, which is followed by a fibrous encapsulation.[10,20–22] The material is not biodegradable, and therefore should persist throughout a lifetime. Results of endoscopic correction of VUR with PTFE approach 90% after a single injection in some series and 94% after subsequent injections.[23,24] Long-term follow-up in a multicentered report indicate a sustained effect for up to 10 years.[25,26] In this multicentered study, the overall success rate in 6216 ureters and 4166 children treated at 18 European centers demonstrated a cure rate of 86% after one to four injections, with an obstruction rate of 0.0003%. In a 17-year follow-up of 247 patients treated with PTFE, Chertin et al. demonstrated a sustained 95% success rate after one to four injections and a 5% recurrence rate, with 1.8% requiring open surgery.[27] In the meta-analysis review by Elder et al. of 33 studies reporting on the results of PTFE, the overall success rate after a single injection for all grades combined was 67%.[28]

Experimental studies done shortly after the introduction of PTFE in clinical reports demonstrated the migratory property of PTFE as a result of a significant percentage of particles being <80 μm.[29,30] These particles become phagocytized and carried to regional lymph nodes or enter into capillaries directly upon injection. Malizia et al. had found particles in lymph nodes and distant organs in an experimental model.[31,32] Particle migration has also been reported in humans,[30,33–35] including, in a speculative report, to a child's cerebral microcirculation and associated with an ischemic stroke.[36] Some clinicians have argued that particle migration is at least partially related to the volume of injection; however, clinical reports indicate that particle migration has occurred with volumes as small as 0.5 mL of PTFE.[37,38]

The potential of carcinogenesis with PTFE and other nonautologous substances has been of concern. Although there has not been direct evidence of carcinogenesis with PTFE in an experimental model,[39] there has been experimental evidence linking injected foreign substances of large particulate size to potential carcinogenesis.[40]

Cross-Linked Bovine Collagen

Cross-linked bovine collagen has been used for multiple medical purposes, such as cardiac valves, hemostatic

agents, sutures, and a soft tissue substitute. It is harvested from bovine hide and treated with pepsin to reduce its antigenicity associated with the telopeptides of the collagen helix. It is composed of 95% type I collagen and 5% type III collagen. It is cross-linked with glutaraldehyde to reduce breakdown after implantation by human collagenases. For human implantation, several products have become available (Contigen, Zyplast, Zyderm, GAX 35, and GAX 65).

Upon injection, collagen causes very little local tissue reaction and no granuloma formation. To variable degrees, there is an ingrowth of fibroblasts and eventual replacement with native collagen.[41–43] The degree to which native collagen ingrowth occurs is thought to determine the potential for long-term cure.

Collagen is injected easily with finger pressure, with no special device required. However, as a result of this relatively low viscosity, precise injection may be more difficult. Preinjection skin testing is necessary, as 3% of patients have a hypersensitivity reaction to collagen, although a negative reaction does not completely eliminate the risk of an allergic reaction.[44] As noted in Table 46.2, the initial success with the endoscopic injection of collagen is similar to that of other materials. However, several reports indicate poor sustained results. Haferkamp et al. reported an initial success of 92% after a single injection in 36 children, with a recurrence of reflux in 91% after 37 months.[50] In a similar study, the recurrence rate was 63%.[51] The use of a more concentrated mixture of 65 mg collagen/mL (GAX 65) has shown promise of a more sustained cure in a report by Frey et al., where a 6-month evaluation postinjection demonstrated more retained volume, 26.9% versus 0.1% for GAX 35.[55] Reunanen reported on 197 ureters treated with endoscopically implanted collagen in which 84% remained without reflux at 4 years follow-up.[46] De Grazia and Cimador reported a 16.8% recurrence rate in 129 refluxing ureters injected, with higher rates of recurrence in the higher initial grades of VUR.[52]

TABLE 46.2 Results of endoscopic treatment of vesicoureteral reflux with collagen

Authors	No. of ureters treated	Percent success, after one injection
Lipsky and Würnschimmel[44]	79	68
Frey et al.[45]	204	63
Reunanen[46]	159	82
Capozza et al.[47]	184	78
Leonard et al.[48]	45	75
Polito et al.[49]	76	74
Haferkamp et al.[50]	21	95
Haferkamp et al.[51]	26	92
De Grazia and Cimador[52]	129	74
Tsuboi et al.[53]	8	—

Source: Modified from Läckgren G et al. *AUA Update Ser* 2003;XXII(Lesson 37):294–9.

Polydimethylsiloxane

This bulking agent is composed of particulate silicone in an injectable mixture of fully vulcanized polydimethylsiloxane (40%) suspended in a water-soluble polyvinylpyrrolidone (60%). The particulate size ranges from 35 to 540 μm (average 209 μm) with 28% <80 μm and 7% <50 μm.[56] It is not surprising, therefore, that studies by Buckley et al.[57,58] and Henly et al.[59] found particle migration to the lungs, kidneys, brain, and lymph nodes after injection in animal models. It has been shown that a particulate size of <80 μm facilitates particle migrations.[31] Shedding of silicone particles with migration has been reported from implanted medical devices.[60] The advantage of particulate silicone is that there appears to be less inflammatory response and granuloma formation, although those findings have not been consistent. Silicone is nonbiodegradable and therefore should be permanent once injected at the UVJ. Similar to PTFE, a ratcheted mechanism is required for injection. The injection of silicone induces an inflammatory response with macrophages and fibroblasts and later ingrowth of collagen.[61]

Silicone has been implicated in autoimmune reactions[29,59] and associated with a possible risk of malignancy,[40,62–64] although the data for the latter have been inconsistent.[65] Multiple studies have demonstrated the reproduced effectiveness of injected particulate silicone to correct reflux.[56] Herz et al. demonstrated a success rate of 81% after a single injection and 90% of ureters after repeated injection with a 12-month follow-up.[66] In a 1-year follow-up study from two centers, van Capelle et al. reported success with the endoscopic implantation of silicone in 155/195 children treated, representing 82.3% of ureters injected one or more times.[67] Aboutaleb et al. compared particulate silicone injection versus extravesical ureteral reimplantation for primary low-grade reflux (grades I–III) in 180 patients, 74 silicone injections, and 106 extravesical reimplantations.[68] Of the injected group, 81% were cured at 3 months and 92% at last follow-up compared with 96% at 3 months and 99% at 1 year in the reimplantation group. There were no complications in the injected population, whereas 7% of the reimplanted group had postoperative complications, including 3.3% (two patients) with transient urinary retention. In summary, silicone appears to be an effective agent for the treatment of VUR. Concerns remain regarding its particle size, and therefore its migratory potential, as noted in experimental studies.

Dextranomer/Hyaluronic Acid Copolymer

Dextranomer microspheres were first introduced by Stenberg and Läckgren in experimental models in which 1 mL was placed into the abdominal wall of rats and into the bladder wall of piglets.[69] At 3 months, the implants became encapsulated, with a 23% reduction of the injected volume. Repeat studies performed with radiolabeled dextranomer spheres demonstrated no evidence of distant migration, lymphadenopathy, mutagenic effect, DNA changes, or tumor development.[70] The larger particulate size of the dextranomer/hyaluronic acid (Dx/HA) copolymer compared with PTFE and silicone is thought to account for the fact that it is not phagocytized, and therefore its lack of particulate migration to distant organs.

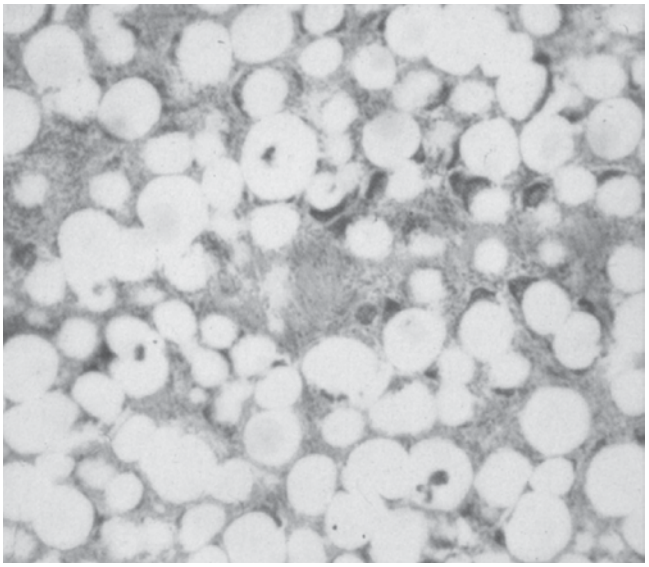

FIGURE 46.7 Ingrowth of native fibroblasts around dextranomer microspheres. (Reproduced from Stenberg et al. *J Urol* 1997;158:1937–41. With permission.)

TABLE 46.3 Results of the endoscopic treatment of vesicoureteral reflux with the Dx/HA copolymer

Authors	No. of ureters treated	Percent success, after one injection
Stenberg and Läckgren[71]	115	69
Capozza and Caione[73]	52	71
Oswald et al.[74]	55	77
Läckgren et al.[14]	334	75[a]
Puri et al.[75]	166	>86
Kirsch et al.[15]	134	72
Capozza et al.[47]	1050	82[a]
Puri et al.[76]	2341	87.1
Kaye et al.[77]	521	90

[a] Reported only after multiple injections.

The Dx/HA copolymer is a solution of cross-linked dextranomer microspheres (80–250 μm in diameter) suspended in a carrier gel of stabilized sodium hyaluronate.[54] Dextranomers have found previous uses in medicine for wound healing, and sodium hyaluronate has been used for eye surgery and joint injection. The Dx/HA copolymer differs from other nonautologous materials, such as PTFE and silicone, in that it is biodegradable. Its volume stability over time results from fibroblast migration and collagen ingrowth between the dextranomer microspheres (Figure 46.7), as the hyaluronate dissipates 12 weeks after implantation.[70] It is injected with a standard syringe mounted on an endoscopic needle with finger pressure. In animal studies, carried out for 3 years, the durability of the spheres has been demonstrated without granuloma formation or calcification.[69,72]

The overall results with the Dx/HA copolymer compare favorably with those of PTFE and silicone, as noted in Table 46.3, which lists the results after a single injection. In a long-term follow-up study by Läckgren et al. of 221 children followed for a mean of 5 years, 68% of patients (75% ureters) maintained grade I VUR or less and 81% (85% ureters) grade II VUR or less at the last VCUG done. Of 49 patients who had a VCUG at 3–12 months, reflux recurred in 13%, 4% of which were grade III or greater.[14] No long-term adverse effects were noted, with 2% developing postoperative UTIs, and early mild postoperative hydronephrosis occurring in four patients, none of whom developed signs of ureteral obstruction. In the largest reported series to date, Puri et al. reported an overall success rate of 87.1% after a single injection in 2341 ureters of 1384 children.[76] No patients developed obstruction and 4.6% had postinjection febrile UTIs. The success rate per grade after a single injection was grade II 100%, grade III 95%, grade IV 75.2%, and grade V 62.4%. While some series, such as that by Kaye et al., have reported such high success rates after single injection to be able to recommend avoiding the postinjection VCUG, most surgeons recommend an ultrasound and VCUG at 3 months postinjection with Dx/HX, and then again should there be a subsequent febrile UTI.[77] In a study comparing the Dx/HA copolymer and silicone, Oswald et al. reported a slightly higher success rate with silicone, but the difference was not statistically significant.[74]

Coaptite

Calcium hydroxylapatite is composed of calcium hydroxylapatite spheres suspended in a water and glycerin mixture with 3% methylcellulose gel. Calcium hydroxylapatite particles are synthetic, and therefore a uniform spherical shape with a narrow range of 75–125 μm. This material represents synthetic bone, and therefore, as a subureteric bulking agent, theoretically should have a limited local reaction and a very durable long-term effect. A clinical trial by Mevorach et al. on 98 patients and 155 ureters with grade II–IV reflux demonstrated reflux resolution in 67% of patients and 75% of ureters, and improvement was noted in 77% of patients and 84% of ureters.[78] Interestingly, five patients in this particular subgroup demonstrated progressive improvement in reflux grade postinjection at 1 year to reflux resolution when evaluated with a VCUG at 2 years. The procedure was tolerated well by all patients, and there were no significant safety issues disclosed. Calcium hydroxylapatite is therefore determined to be a safe, durable, and effective material for the endoscopic treatment of reflux, although at this time clinical trials are still being evaluated by the FDA.

Polyacryl Polyalcohol Copolymer

Experience with a nonbiodegradable material, polyacrylate polyalcohol bulking copolymer, has been reported by some centers.[79,80,81] This substance is synthetic with an average diameter of 300 μm, which should prevent distal migration. Success rates for uncomplicated VUR have ranged from 83% to 92.1%, with a low rate of obstruction

(1%–2%). Long-term data with late follow-up VCUG have not been reported to date. The anticipated long-term success comes from its nonbiodegradable property and the formation of a pseudocapsule.

Autologous Materials

Autologous materials have the appeal of not having the concern of a foreign body reaction to the injected mound. The disadvantage, however, is the need for a harvesting step, which, with all materials tried to date in the pediatric population, requires an additional anesthetic. These autologous materials must behave as free grafts, and therefore are subject to the physiology of graft survival. To date, the autologous materials that have been tried are collagen, fat, and chondrocytes.

Chondrocytes

Following demonstration that the harvesting and subsequent implantation of autologous chondrocytes resulted in viable chondrocytes, first in the mouse model and later in the pig model by Atala et al.,[82,83] Diamond and Caldamone used harvested chondrocytes in the human model.[84,85] Chondrocytes were harvested from the posterior auricular cartilage, grown in culture for 6 weeks, suspended in an aqueous mixture of alginate and calcium salts, and subsequently injected at the UVJ. Long-term results of 47 ureters with grade II–IV VUR demonstrated an 80% cure rate at 3 months and an 86% cure rate at 1 year following one or more implantations. In those children requiring a subsequent open ureteral reimplantation, no viable chondrocytes were identified, however. It was unclear whether the failure to correct the reflux was attributed to a failure of chondrocyte survival, or whether this was a more universal effect. In those children who underwent a second injection or open reimplantation after a failed injection, the most common findings were shifting of the materials and a loss of material volume.[85]

Fat

Autologous fat has been used as an implant for correction of reflux. It was initially reported in an experimental model by Matthews in 1994, followed by clinical reports by Palma and Chancellor.[86–88] In follow-up studies at 3 months postimplantation, reflux persisted in 70% of Chancellor's study group and 83% of Palma's group. Viability appears to rely on vascular ingrowth to the injected cells, and therefore small volumes injected appear to be more effective in survival. In the rabbit model by Matthews, there was a 25%–100% loss of volume postinjection in 47% of sites injected.[86]

Collagen

Cendron et al. reported on the use of autologous collagen as an injectable material for correction of VUR.[89] The rationale for the use of autologous collagen is to improve the longevity of bovine collagen preparations, as well as to avoid the hypersensitivity potential. Collagen fibers were isolated by centrifuge from the dermis. In an experimental study, collagen integrity was demonstrated at 50 days.

Muscle

Autologous bladder muscle cells have been used in an experimental study to correct reflux.[90] Muscle cells were harvested from the bladder, coupled with an alginate mixture, and reinjected through a 21-gauge needle. Cell survival was demonstrated in a short-duration study.

Cumulative Results

Endoscopic treatment for VUR in children has a high success rate (Table 46.4). The success rate is universally proportional to the grade of reflux treated (Table 46.5). Multiple injections are advantageous in increasing the success rate, and prior endoscopic material implantation does not appear to significantly alter the open surgical success rate.

Special Considerations

Neurogenic Bladder

A significant number of patients, upwards of 50%, with spina bifida have associated VUR. This can be a cause of significant morbidity and renal damage in this population. The mainstay of management of VUR in association with a neurogenic bladder has been modulation of bladder pressures and frequent complete emptying. This is usually

TABLE 46.4 Overall resolution rate after single injection for all reflux grades based on ureter and material

Agent	Number in studies	Sample	Percent resolution
Tetrafluoroethylene	33	3616	66.9
Collagen	10	947	56.9
Dextranomer	3	385	68.7
Polydimethylsiloxane	8	347	76.5
Chondrocytes	1	47	50.5
Blood	1	13	5.0

Source: From Elder JS et al. *J Urol* 2006;175:716–22.

TABLE 46.5 Overall resolution rate after single injection based on reflux grade by ureters for all materials

Grade	Number in studies	Sample	Percent resolution
I	16	117	78.5
II	18	444	78.5
III	22	477	72.3
IV	17	172	62.6[a]
V	9	25	50.9[a]

Source: From Elder JS et al. *J Urol* 2006;175:716–22.
[a] Grades IV and V significantly decreased with respect to grades I and II.

TABLE 46.6 Results of reported series of the endoscopic treatment of vesicoureteral reflux in children with neurogenic bladder

Authors	Material	No. of ureters	Success rate after one or more injections	Recurrence rate per corrected ureter
Haferkamp et al.[51]	Collagen	26	24/26	15%
Granata et al.[91]	Polytetrafluoroethylene	40	72.5%	2/29
Engel et al.[92]	Polytetrafluoroethylene	60	56.7%	—
Misra et al.[93]	Polydimethylsiloxane	69	82%	4/57
Yokoyama et al.[94]	Collagen	13	100%	5/13
Sugiyama et al.[95]	Polytetrafluoroethylene	4	75%	—
Kaminetsky and Hanna[96]	Polytetrafluoroethylene	20	70%	—
Dewan and Guiney[97]	Polytetrafluoroethylene	29	23/29	4/23
Puri and Guiney[98]	Polytetrafluoroethylene	15	12/15	—
Perez-Brayfield et al.[99]	Dextranomer	9	78%	—

accomplished by a combination of intermittent catheterization with or without the addition of anticholinergic therapy and/or suppressive antibiotics. When children fail this regimen, treatment has been bladder augmentation with or without ureteral reimplantation. Some have advocated the addition of endoscopic correction of reflux to the armamentarium for management of VUR in the setting of the neurogenic bladder (Table 46.6). Technically, this can be more difficult to perform because of the trabeculation of the bladder, and a ureteral catheter in the orifice at the time may facilitate injection. However, in spite of these difficulties, success has been reported in up to 90% of cases after multiple injections.[93,98,100,101] Engel et al. reported success in 57% of reflux in ureters after a single injection of PTFE and 62% after a second injection.[92] They compared this with their open surgical population, in which they were able to achieve an 84% success rate in 30 patients undergoing ureteral reimplantation. Haferkamp et al. found that the long-term success rate using collagen (GAX 35) was only 15% of treated units after 24 months.[51] Part of that falloff in success rate could be a result of the degeneration of collagen, but it also may result from the inherent neurogenic disorder. It is imperative that once these children are treated endoscopically or with open surgery, continued bladder management is carried out in order to prevent long-term complications, such as the recurrence of reflux or functional UVJ obstruction. Similarly, Dewan and Guiney reported that 4 of 23 successfully treated ureters recurred.[97] Granata et al. reported a comparative study on surgical and endoscopic correction of reflux in children with a neurogenic bladder.[91] They found an overall success rate of 72.5% using PTFE, compared with 95.5% when a Cohen cross-trigonal ureteroneocystostomy was performed. They found that 2 of their 29 ureters that were cured with the endoscopic approach recurred with VUR; however, both were treated successfully by a repeat endoscopic procedure. There were no recurrences observed in the patients cured by open reimplantation. In a meta-analysis recorded by Elder et al. of 10 articles, there was a significantly lower rate of success of the endoscopic approach in the neurogenic bladder (53.5%) versus the nonneurogenic bladder (74.2%).[28] However, more recently, on both univariate and multivariate analyses, Routh et al. found that neurogenic bladder was not a predictor of failure.[102] It is likely that surgical experience with endoscopic injection for VUR in the neurogenic bladder is a major variable in success rates.

Dysfunctional Voiding

Studies by Frey et al.,[41] Trsinar et al.,[103] and Capozza et al.[47,104] have implicated undisclosed dysfunctional voiding as a cause of failure of endoscopic correction of VUR. In each of these cases, the authors found displacement of the mound to be a common occurrence using either collagen or dextranomer microspheres. In each of these studies, however, the diagnosis of dysfunctional voiding was based on clinical history and not urodynamic findings, representing some limitation to their conclusion. The implication from these studies, therefore, would be to control or at least stabilize the dysfunctional voiding prior to the endoscopic correction of the reflux. Other studies have not found a higher failure rate or recurrence rate following endoscopic correction for VUR in dysfunctional voiders.[102,105] Several studies have pointed out that management of dysfunctional voiding improves the spontaneous resolution of reflux and decreases the need for ureteral reimplantation.[106,107] Läckgren and Stenberg noted, however, that when the endoscopic correction of reflux in children with dysfunctional elimination syndrome was undertaken, they found an overall cure rate of 65% across all grades of reflux, indicating no particular difference as to whether preinjection bladder retraining had been undertaken.[108] Of 35 patients that were cured of their reflux on a single injection, 8 continued to have evidence of minor bladder dysfunction, whereas 27 appeared to have completely resolved their symptoms of bladder dysfunction. This may indicate a potential role of the reflux in either the causation or the promotion of bladder dysfunction in this particular population.

Duplicated Systems

More experience is being gained in the use of injectable materials for duplicated systems. At one time, a duplicated

system was considered to be a relative contraindication to the use of injectable material;[109] however, several reports have now indicated that with experience, the success rate for the endoscopic correction of reflux in the duplicated system approaches that of a single system. Miyakita et al.[110] reported on their results with the use of PTFE in both partial and complete duplication. Their success rates were 87% in partial duplication and 59% in complete duplication. Similarly, Steinbrecher et al. reported a cure rate of 68% in completely duplicated systems using PTFE.[111] Dewan and O'Donnell reported on 32 children with duplex systems and VUR treated endoscopically with PTFE.[112] They were able to cure VUR in 21/32 patients. In the meta-analysis by Elder et al., the success rate of endoscopic correction for duplicated systems was 50% compared with 73% for nonduplicated systems.[28] Perez-Brayfield et al. reported a 73% success rate in using dextranomer microspheres for the endoscopic correction of reflux and completely duplicated systems.[99] Läckgren et al. reported on the use of the Dx/HA copolymer and duplicated systems, and found a 63% success rate, defined by improvement to grade 0 or I.[113] In a study of Dx/HA injection for VUR in the setting of bladder and ureteral anomalies, Routh et al. demonstrated on univariate analysis that ureteral duplication was a predictor of injection failure. However, in a multivariate analysis controlling for VUR grade, subureteric injection technique, and surgeon experience, there was no difference in the failure rate for duplicated systems compared with single systems.[102]

It should be pointed out, however, that the technique of the injection varies with the anatomy. For those completely duplicated systems in which there is wide separation of the ureteral orifices, and therefore more likelihood to reflux just to the lower pole, separate injections under each orifice are recommended. However, for those duplicated systems where the orifices are closely approximated, a single injection may suffice (Figure 46.7).

Aboutaleb et al. compared the results with polydimethylsiloxane injection versus open surgery for the treatment of VUR in duplex systems.[114] The open surgical approach for reflux in this study was extravesical common sheath ureteral reimplantation. The endoscopic injection of polydimethylsiloxane was performed in 15 patients with 22 refluxing units. The success rate for the endoscopic correction was 68% at 3 months and 82% at 12 months, with one patient developing contralateral VUR. There were no cases of de novo hydronephrosis or UTIs postoperatively. This compared with the success rate of extravesical common sheath ureteral reimplantation of 96% at 3 months and 97% at 15 months. The authors concluded that whereas injection therapy was highly successful in patients with low-grade VUR in duplex systems, it still fell short of the open surgical cure rate.

Paraureteric Diverticulum with VUR

Bladder diverticulum can be found in association with VUR. Whereas those diverticulae that are small have a spontaneous resolution rate similar to that of primary VUR, moderate to large diverticulae, which usually lie lateral and cephalad to the ureteric orifice, will often drag the orifice into the diverticula on filling or voiding. This relationship portends a poor spontaneous resolution rate. The presence of a paraureteric diverticulum that is associated with reflux presents a significant challenge to the accurate placement of material at the UVJ endoscopically. Perez-Brayfield et al.[99] report on six such cases, with a success rate of 67% using the Dx/HA copolymer. It appears that with experience, the presence of a paraureteric diverticulum represents only a relative contraindication to endoscopic treatment. Puri and Läckgren (personal communication) have stated that a modified technique to this anatomy is needed, in which the material is injected beneath the ureteric orifice for a longer length into the diverticulum.

Refluxing Ureteral Stump

There have been isolated reports of success using the endoscopic approach for the refluxing ectopic ureter, refluxing ureteral stump, and reflux after transurethral ureterocele incision.[99,115,116] The results in the ectopic ureter, however, have been very disappointing to date.[99] This may also be true for the refluxing stump, which is often ectopic at or below the bladder neck, although there have only been a few reported cases.[115,116]

Failed Ureteral Reimplantation

From the 1997 report of the American Urological Association Pediatric Vesicoureteral Reflux Guidelines Panel, the success rate for correction of reflux by open ureteral reimplantation ranges from 80% to 99%, based on the grade of reflux.[117] Overall, the incidence of persistent reflux is generally 2% and the incidence of ureteral obstruction is 2%. Reoperation for the failed ureteral reimplantation can be a difficult procedure, with a significant complication rate.[118] There have been reports on the use of the endoscopic approach to reflux correction for the failed ureteral reimplantation.[99,119–121]

Kumar and Puri reported on 31 children with persistent reflux with 40 persistently refluxing units after failed ureteral reimplantation.[119] These patients represented a diverse group that includes primary reflux, duplicated systems, reflux secondary to neuropathic bladder, posterior urethral valves, ureterocele, bladder exstrophy, and UVJ obstruction. Twenty-seven of 40 persistently refluxing units were cured after a single injection of PTFE, 7 refluxing units required two injections, and 4 required three injections for correction of the reflux. Failure to correct reflux by endoscopic correction was noted in two ureters of one patient with bladder exstrophy. In the report by Gaschignard et al., 1 of 12 patients developed a late meatal stricture, occurring 2 years after endoscopic correction following a failed ureteral reimplantation.[121] Perez-Brayfield et al. reported on 17 patients who had failed open surgical correction of reflux. The success rate with endoscopic correction in this group was 88%.[99] Capozza et al. reported success in 12 of 18 ureters with endoscopic treatment after failed ureteral reimplantation.[47] In a review of 9 studies and 80 ureters, Elder et al. reported a cumulative success rate of 65% for endoscopic injection after failed ureteral reimplantation, compared with 74% in the nonreimplanted ureter.[28]

Complications

The risk–benefit ratio for endoscopic correction of reflux remains very low. Specific complications related to inherent material properties have been mentioned, such as particle migration with PTFE and with polydimethylsiloxane. Other specific concerns have been raised, such as malignant degeneration with PTFE or the development of connective tissue disorders with polydimethylsiloxane.[64,122–125]

More generic complications, such as ureteric obstruction, have been reported infrequently. Engel et al. reported obstruction in a single ureter after the endoscopic implantation of PTFE in their series of 60 injected ureters.[92] In the reported series by Capozza et al. of 1244 patients injected with a variety of materials, 8 (0.5%) developed temporary obstruction, 2 requiring a double-J stent.[47] In their meta-analysis, Elder et al. noted a very low incidence of de novo injection hydronephrosis (Table 46.7).[28] In a report by Mazzone et al. of a series of Dx/HA injections in 87 ureters (45 patients), 5 ureters (5.7%) in 5 patients developed significant obstruction requiring intervention, 4/5 were transient but symptomatic (2 requiring percutaneous nephrostomy and 2 ureteral stenting), and 1 required ureteral reimplantation.[126] Other outcomes, such as UTIs, febrile or not, do not appear to occur with an increased frequency over that seen with open ureteral reimplantations: 6.4% in a meta-analysis of 11 studies, 0.7% for febrile UTI, and 6% for cystitis.[28]

The development of contralateral de novo VUR following reflux correction may be troublesome.[127] Studies by Ross et al. indicate a 35% risk of contralateral VUR after unilateral open correction if there has been a remote history of contralateral VUR.[128] Hoenig et al. reported an incidence of contralateral VUR occurring in 17% of cases after unilateral open correction similar to that reported by other surgeons.[127,129–131] Following the endoscopic correction of reflux with PTFE, Kumar and Puri reported the contralateral de novo VUR rate to be much lower, at 7%.[132] Similarly, Kirsch et al. reported its occurrence in 4.5% with the Dx/HA copolymer.[15] This lends credence to the theory of trigonal distortion during open reimplantation rather than a pop-off mechanism theory as the etiology for de novo postoperative VUR.[133]

Controversy still exists as to whether injection of the contralateral nonrefluxing orifice is warranted in unilateral VUR. As other studies have shown for ureteral reimplantation, Chertin et al. demonstrated recurrence of previously resolved VUR in the contralateral ureter after unilateral injection in 14 of 15 children.[134] Approximately half of the children with contralateral reflux recurrence became symptomatic with breakthrough UTIs. However, de novo contralateral VUR (in the setting of no history of prior VUR) is of relatively low incidence, of low severity when it occurs, and generally asymptomatic. In a study by Menezes et al., 10% of 662 patients developed contralateral de novo VUR after unilateral injection, ranging in grade from I to IV, with 90% grade III or less.[135] Routh et al. reported on a series of patients with unilateral VUR in which an assessment was made of the morphologic cystoscopic appearance of the contralateral nonrefluxing orifice.[136] If subjectively the contralateral orifice appeared abnormal, prophylactic injection with Dx/HA was done. Of those contralateral orifices injected, 9% developed de novo VUR compared with 13% of those that were not injected, suggesting that the subjective assessment of the cystoscopic appearance of the nonrefluxing contralateral orifice as a determinant of prophylactic injection is of little benefit. Therefore, considering cost, it would seem unnecessary to prophylactically inject a nonrefluxing contralateral ureter.

TABLE 46.7 De novo postinjection hydronephrosis based on material used: A meta-analysis

Material	Denovo hydronephrosis/ total number[a]	No. requiring intervention[a]
Polytetrafluoroethylene	34/3616	19
Collagen	2/947	0
Polydimethylsiloxane	4/347	3
Dextranomer	2/385	2

[a] Data from Elder JS et al. *J Urol* 2006;175:716–22.

Recurrence of Vesicoureteral Reflux

Recurrence after proven correction of reflux remains an issue with certain materials. The difficulty is determining a firm and reliable figure for this, as only selected series have performed a VCUG beyond the initial negative study. In addition, one must distinguish between a maintained clinical cure (i.e., no febrile UTIs) and a proven long-term cure by a negative VCUG. Chertin et al. reported on 247 patients who were treated for VUR with PTFE and followed for 17 years.[27] They reported a recurrence rate of 5%, with 1.8% requiring open ureteral reimplantation. Capozza et al. reported on their long-term experience with bulking agents—specifically PTFE, collagen, and dextranomer—in 1244 patients, all of whom had a VCUG at 3 and 12 months postinjection. They found that a significant percentage of those patients who relapsed had evidence of voiding dysfunction by micturation questionnaire.[47] Läckgren et al. reported their long-term results with the use of the Dx/HA copolymer in 221 children who had a VCUG at 3 and 12 months postinjection.[14] In addition, a later VCUG was performed in 49 patients 2–5 years after initial treatment. Reflux on the late VCUG occurred in 13% of those previously cured. It is unclear how many of those late recurrences were symptomatic.[14]

Several series have reported on the recurrence rate of VUR in children with postinjection febrile UTIs. In a series by Chi et al. of 15 patients post–Dx/HA injection with a febrile UTI, VCUG revealed recurrent VUR in 7.[137] Sedberry-Ross et al. reported that 27% of their patients treated successfully endoscopically with Dx/HA had a febrile UTI (12/45).[138] Ninety-two percent (10/12) were found to have recurrent reflux when evaluated with a cystogram after their infection. In analyzing the 12 patients who had postinjection febrile UTIs, most of them had multiple predictive factors of UTIs, including preoperative febrile UTIs, dysfunctional elimination, and existing renal cortical defects on dimercaptosuccinic acid (DMSA)

scanning. It seems clear, therefore, that those patients who are likely to have a febrile UTI after successful endoscopic treatment for VUR are predictive from analyzing preinjection risk factors. In the Swedish Reflux Trial, Holmdahl et al. demonstrated a 20% recurrence rate of dilating VUR in asymptomatic children studied 2 years after injection.[139] Similarly, Lee et al. performed a follow-up VCUG on 150 asymptomatic children 1 year after a successful endoscopic treatment with Dx/HA and found recurrence of reflux in 26%.[140]

Haferkamp et al. reported on the use of a second collagen injection in 16 children with 21 ureters with a failed first injection.[51] They found that the reflux was cured after a second injection in 17/21 ureters. Of those cured with a second injection, a repeat VCUG was performed every 6 months, with a mean follow-up of 11 months. Of these patients, eight ureters remained reflux-free, whereas in nine units the reflux recurred. The authors noted that the interval to recurrence of reflux was longer after the second injection than with the first injection. In a similar report, Haferkamp et al. found that of 55 renal units successfully treated with collagen, only 5 (9%) remained reflux-free after 37 months of follow-up.[51] Other studies have shown a more modest recurrence rate of 11%–16%.[52] In a report of 132 children, Frey et al. reported late reflux recurrence in 11.3% of 204 renal units treated with GAX 35 collagen.[45] In the meta-analysis study by Elder et al., the probability of recurrence for all agents used was 8%.[28] In a review of contemporary series of multiple bulking agents for VUR correction with at least a 1-year follow-up VCUG, including their own experience, Chertin and Kocherov determined that Dx/HA has the highest recurrence rate (3.9%–26%).[141]

The lowest recurrence rate was with PTFE. Overall, it appears that collagen carries a higher recurrence rate than other bulking agents that have been followed with a VCUG beyond 1 year postinjection, with the lowest recurrence rate from PTFE.

Reasons for Failure of Endoscopic Treatment

Whereas most series have demonstrated a high success rate for the endoscopic subureteric injection for the treatment of VUR, very few have discussed the reasons for failure. The mechanism of failure of endoscopic correction of reflux can be divided into three categories:

- Technical factors
- Bladder dynamics issues
- Individual physical properties of the particular material used

Technical factors include anatomic abnormalities of the UVJ or bladder, including duplicated systems; paraureteric diverticulum; a trabeculated bladder, from either neuropathic origin or obstructive origin, be it functional or anatomic; or a previously reimplanted ureter. In addition, the position of the orifice can certainly be influenced by the degree of fullness of the bladder, making the injection zone for the material larger or smaller. It is also theoretically possible that—with the bladder relatively empty at the time of the injection, as is the standard recommendation—when the bladder fills, the mound and orifice may not have the same relationship to each other.

Elevated bladder pressure that is seen in the neurogenic bladder, the previously obstructed bladder, or dysfunctional voiding may affect outcomes after injection therapy. Capozza et al. implied that voiding dysfunction could contribute to endoscopic injection failure.[47] They theorized that elevated intravesical pressures could displace or shift the injection mound or cause migration from the original site of implantation. They found, in retrospect, that a high percentage of those patients who had failed initial endoscopic treatment had evidence of voiding dysfunction on clinical evaluation. Therefore, they advocated that voiding dysfunction be addressed prior to undertaking the endoscopic treatment for reflux. Trsinar et al. also observed displacement of failed injection mounds and theorized that this was due to voiding dysfunction, although there were no urodynamic studies or voiding diaries presented.[103]

Specific material properties may also play a role in the failure of endoscopic correction of reflux. Materials that have been utilized have a variable degree of longevity. Loss of material can occur by absorption of the carrier substance that is used for the specific material, as seen with glycerol for PTFE, hyaluronic acid with dextranomer particles, alginate solution with chondrocytes, or aqueous gel with calcium hydroxylapatite. These materials will be absorbed in a variable amount of time from the implant site, decrease the site of the injection mound, and therefore possibly hinder the mechanism for ureteral closure or insufficient support of the intramural ureter. In addition, there is an intrinsic material biodegradability that plays a role with certain substances. Collagen is known to have a significant loss of volume over time, and its long-term success is thought to be due to the development of natural collagen to replace the resorbed injected collagen. Haferkamp et al.[51] demonstrated a low rate of long-term success with collagen in that after 37 months, only 5 out of 57 ureters previously corrected with a single injection remained cured. Similarly, dextranomer microspheres have some degree of biodegradability, which eventually should be replaced by the ingrowth of native fibroblasts. McMann et al. performed sonographic volumetric analyses on injected Dx/HA mounds and found a 20% volume loss, most of which occurred within the first 2 weeks postinjection.[142]

The ability of a particular material to weld at the injection site may be a factor in the long-term success as well. Materials that tend to create an inflammatory response may be more likely to stick to the site of the injection. The viscosity of the material may also be a factor that may or may not allow it to easily leak through the needle track of the injection site. When dealing with autologous materials, as previously mentioned, free graft issues come into play. The ability of fat, collagen, muscle, or chondrocytes to grow in their new location may require some of the same principles of imbibition and inosculation that one sees with larger tissue graft physiology. This was shown in the report by Diamond et al. on autologous chondrocytes, in which those mounds that were explanted at the time of ureteral reimplantation failed to demonstrate viable chondrocytes.[143]

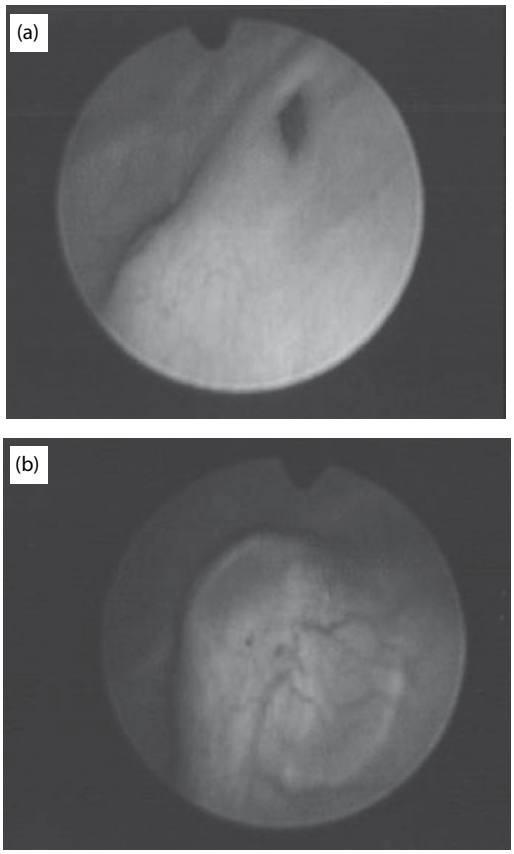

FIGURE 46.8 (a) Duplicated left ureters with lower-pole reflux. (b) Mound under lower-pole refluxing orifice.

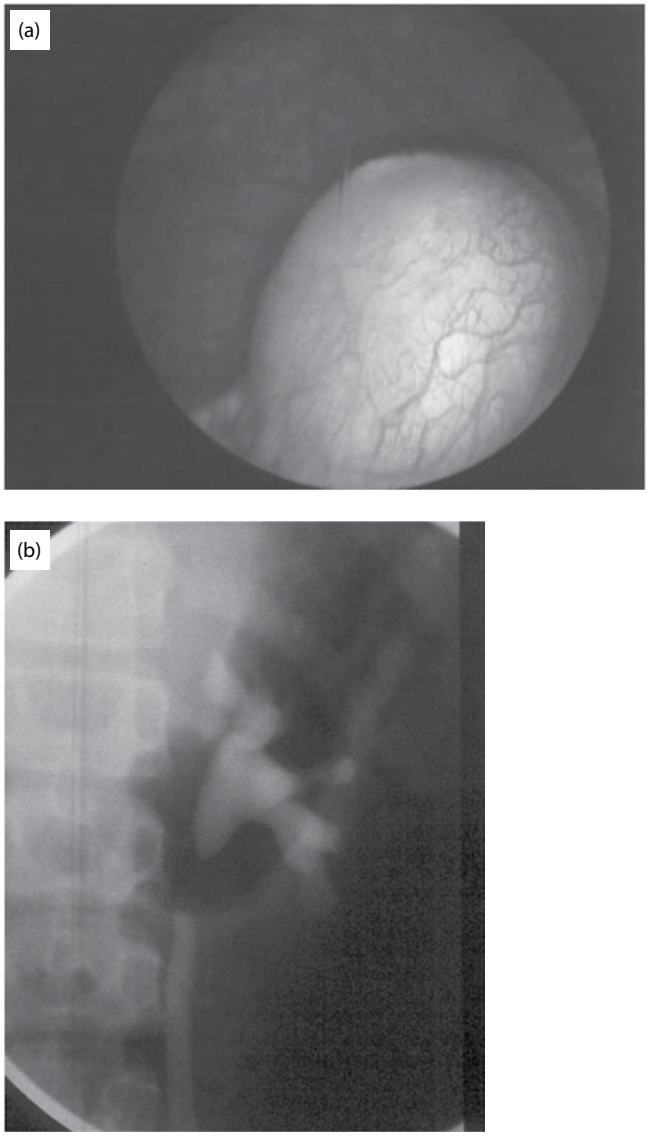

FIGURE 46.9 Mound shifting or displacement. (a) Appearance of mound and left ureteral orifice at time of initial injection. (b) Appearance at time of reinspection for persistent VUR on a VCUG.

Several studies have documented that in those cases where observation of the injection site was possible after a failed implantation, displacement appeared to occur quite frequently (Figure 46.8). In a series reported by Diamond et al. on cystoscopic examination of patients who had failed subureteric injection with autologous chondrocytes, it was noted that 35% had mound shifting, 25% had shifting and volume loss, and 13% had isolated volume loss. It appeared that the most frequent direction of mound shifting was distally and medially toward the bladder neck from the original injection site.[143] Eleven percent of their population, however, were classified as indeterminate; i.e., there was failure on postoperative VCUG to resolve the reflux, but the appearance of the mound on cystoscopic or intraoperative inspection was perfectly normal (Figure 46.9). Other studies also found that either mound displacement or absence of a mound was the most common cause of failure on reinspection either cystoscopically or by open surgery of failed primary injections.[66,144,145]

Fewer studies have focused on failures from the injection of the dextranomer microspheres. Capozza et al. reported on 45 failures with the Dx/HA copolymer, and found 60% had mound displacement and 33% had absence of the mound on reinspection.[146] They reported a high percentage of their cases with failed dextranomer microspheres and suspected high intravesical pressures noted by voiding diaries. In two cases, however, there was a unilateral cure and contralateral mound displacement. It is uncertain as to whether this represented a technical failure or an anatomic failure. However, it is unlikely that they represented abnormal bladder physiology. Kirsch et al.[15] reported on 18 patients who underwent reinjection for primary failures and found that 61% had shifting of the mound away from the injection site. In the remainder of patients, the mound was either absent or present, and therefore indeterminate.

Higham-Kessler et al. reported a multi-institutional review of failures after Dx/HA injections for VUR.[147] Eighty patients (97 ureters) who failed a single injection underwent mound observation prior to a second injection or at the time of open surgery. They found that in those who had a mound abnormality, in 49% the mound had shifted, in 22% the mound was absent, and in 10% there

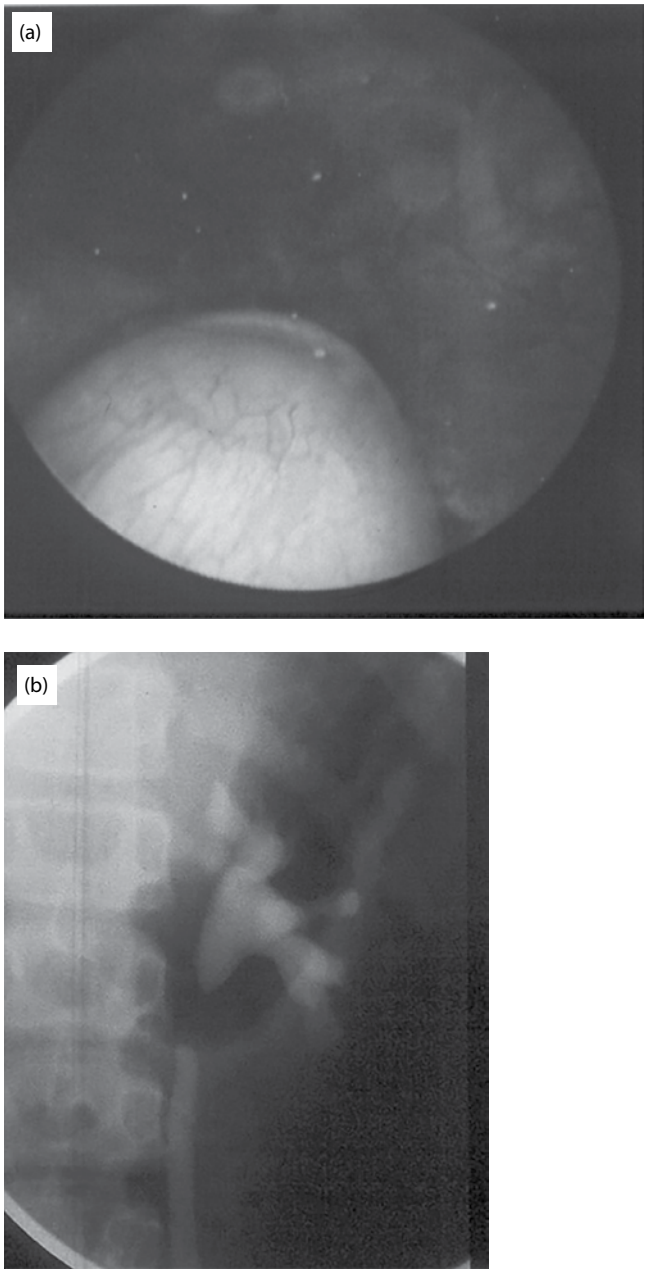

FIGURE 46.10 Perfectly injected mound with persistent VUR on a VCUG classified as an indeterminate failure. (a) Mound on recystoscopy. (b) VCUG demonstrating left VUR.

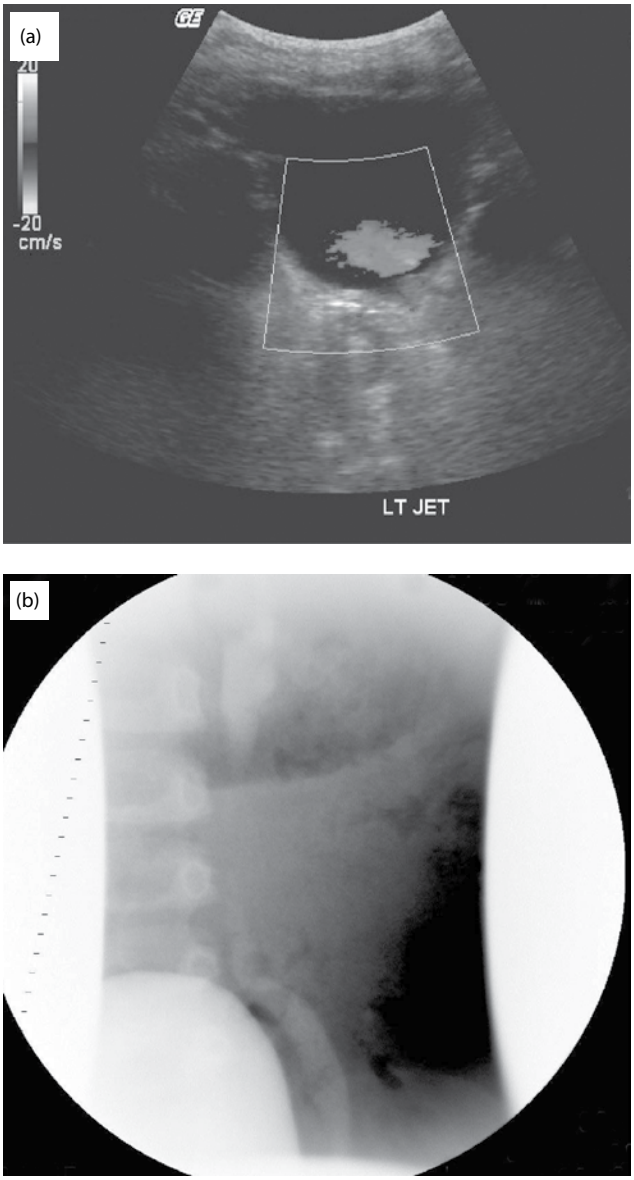

FIGURE 46.11 (a) Ultrasound 3 months post-Dx/HA copolymer injection with normally positioned left mound and ureteral jet exiting from top of mound. (b) A VCUG 3 months postinjection demonstrating persistent left VUR.

was a significant mound volume loss. In 15%, the mound was in the perfect location in spite of persistent VUR (Figure 46.10). Other studies have also confirmed that a malpositioned mound can be seen in both successful and unsuccessful injections, implying that other factors, such as bladder dynamics and UVJ maturation, may be at play in the success of an endoscopic injection (Figure 46.11).[148] In a study by Dave et al., multiple variables were analyzed with respect to injection success.[149] On multivariate analysis, higher injection volume, surgical experience, and treatment of lower UTI symptoms were associated with a higher success rate of VUR correction. Similarly, Kirsch identified several factors affecting the success of endoscopic injection for VUR, citing injection volume, surgeon experience, and the HIT as important variables.[150] Additionally, it has been advocated that since a normal mound appearance alone does not predict successful correction of VUR, loss of ureteral hydrodistention is a more objective measure of a successful injection. Sorensen et al. studied injection volume using a Pediatric Health Information System (PHIS) database over the period 2003–2008 and found a threefold increase in the number of patients in which three or more vials of Dx/HA were used.[151] Interestingly, while there was an increase in the average vials used in all institutions, the most pronounced was at those institutions doing the most cases, implying a directed plan to inject higher volumes of material.

CONCLUSION

With a technology that is reproducible and at least a single agent that is widely available for endoscopic correction of reflux that appears safe, the obvious question that is raised is, where does this fit in the management of children with VUR? This question must be addressed in light of the present-day concerns for the use of long-term antibiotics with growing patterns of resistance. Studies have questioned the effectiveness of long-term antibiotic prophylaxis,[152] and the potential for long-term complications.[153]

The use of the Dx/HA copolymer has been shown to be a cost-effective alternative to open surgery for persistent VUR in children on a prophylactic antibiotic program.[154] However, publications by Benoit et al. analyzed the cost-effectiveness of Dx/HA compared with traditional management with antibiotic prophylaxis or open surgery.[155,156] Dx/HA appeared to be more cost-effective than ureteral reimplantation for lower grades of reflux in children meeting the criteria for traditional surgical therapy. However, in cases of increasing grades of VUR, which require an increased volume of Dx/HA, injection therapy loses its cost-effectiveness. Regarding antibiotic prophylaxis, in theoretical models simulating clinical scenarios, up-front injection therapy with Dx/HA was not as cost-effective as traditional management consisting of ureteral reimplantation for those failing antibiotic prophylaxis.

The effectiveness of endoscopic therapy requires that its approach be presented to parents as an up-front treatment in lieu of antibiotics. However, there have been a paucity of studies looking at long-term outcomes in a comparative analysis between antibiotic therapy and endoscopic correction. Studies that have shown endoscopic treatment with the Dx/HA copolymer to be more effective than antibiotic prophylaxis have often been of relatively short duration, raising the criticism of an adequate clinical trial. Additionally, is the outcome of VUR resolution the only outcome we should be concerned with? These questions will only be answered with multivariant prospective trials, which are difficult to perform in children. It is possible that endoscopic correction may change our approach to children with secondary reflux as well. Traditionally, children with neurogenic bladders or dysfunctional voiding and VUR are approached by managing the bladder dysfunction initially and reserving correction of VUR for those children with upper tract deterioration or breakthrough pyelonephritis. One could argue, however, as this population has a high rate of breakthrough UTIs and renal scarring,[157] for correcting the VUR endoscopically while ongoing and often tedious efforts at bladder rehabilitation are undertaken, thus protecting the upper tracts from pyelonephritis and potential scarring. This approach may have merit in light of the observation of Läckgren and Stenberg on the improvement in dysfunctional voiding in children treated primarily with endoscopic injection of the Dx/HA copolymer without bladder management, implying that the reflux itself may contribute in some way to the abnormal bladder function.[108] Clinical trials in these scenarios would be most valuable.

In the integration of new technology and new concerns in the management of children with VUR, it would be helpful if we were better able to identify groups at high and low risk for renal scarring and tailor our management accordingly. With further progress in clinical research of VUR, we may be able to withhold therapy for certain low-risk groups, while taking a very aggressive approach, by either endoscopic correction or open ureteral reimplantation, for patients at high risk of renal scarring from VUR and infection.

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Section 5

The Bladder and Prostate

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CHAPTER 47

Basic Science of Prostatic Development

Ellen Shapiro and Hongying Huang

INTRODUCTION

The fetal prostate is a proliferative organ and represents an excellent model for the study of morphogenesis, hormonal imprinting, and epithelial–mesenchymal interactions in the genitourinary tract. Events associated with fetal prostate development and in utero influence may alter growth in adulthood and will likely provide insights into the mechanisms giving rise to benign and malignant growth of the prostate.

EMBRYOLOGY OF THE PROSTATE

The prostate develops from the endodermal urogenital sinus (UGS), which is derived from the terminal end of the hindgut or *cloaca*, which is Latin for "sewer." Septation of the cloaca by the urorectal septum begins at about 28 days of gestation.[1] The rectum and primitive UGS form by the 44th day. The primitive UGS proximal to the mesonephric duct develops into the vesicourethral canal, whereas the region distal to the mesonephric duct becomes the definitive UGS. The UGS adjacent to the bladder (pelvic urethra) differentiates into the lower portion of the prostatic and membranous urethra.[2]

Prostate growth and development are dependent on androgen production by the fetal testes, which begins at about the eighth week of gestation.[3] Unlike development of the Wolffian duct (WD) derivatives, which are dependent solely on testosterone, the differentiation of the UGS is dependent on the 5α-reduced form of testosterone, dihydrotestosterone (DHT). DHT is essential for the growth and development of the prostate.[3,4,12,15] By 10 weeks, the prostatic ductal network develops from solid epithelial outgrowths, or prostatic buds, which evaginate from the endodermal UGS immediately below the bladder and penetrate into the surrounding urogenital mesenchyme (UGM).[5]

The prostatic ducts rapidly lengthen, arborize, and canalize. By 13 weeks, 70 primary ducts are present and exhibit secretory cytodifferentiation.[5]

Within the fetal prostate lies the utricle. Although the embryological origin of the utricle is thought to be a remnant of the fused caudal ends of the Müllerian ducts (MDs), compelling evidence from Shapiro et al. indicates that the utricle forms as an ingrowth of specialized urothelium lining the dorsal wall of the UGS.[6] Utricular formation is occurring during complete caudal MD regression (Figure 47.1). Since utricular development from the UGS is similar to that of the vagina in the female fetus, it has been appropriately referred to as the "sinus vagina." Since testosterone inhibits the formation of the lower vagina in the female, formation of an enlarged utricle in some males with severe hypospadias may be due to inadequate virilization of this region of the UGS at a critical time during early gestation.[7]

Hofkamp et al. studied the ACI (August × Copenhagen) rat, which is a model for urogenital anomalies, including renal agenesis and ipsilateral hypoplasia of the WD derivatives.[8] These investigators focused on prostatic development in those ACI rats with ipsilateral hypoplasia of the WD structures. They showed that those affected ACI rats had a significant decrease in total fetal prostate volume (40%, $p < 0.005$) and region-specific differences when compared with normal control ACI rats that had no WD anomalies. Interestingly, the ipsilateral testis was devoid of normal seminiferous tubules, while the contralateral testis was completely normal.

WDs are stabilized by androgens, and the prostate is dependent on the diffusion of testicular androgens via ejaculatory ducts (EDs) and the vas deferens for growth and stabilization. Prostatic budding occurs in response to an androgen-dependent secretion of growth factors by the periurethral mesenchyme.[9] Therefore, alterations in WD development can potentially limit the levels of androgens required for normal induction of prostatic budding and morphogenesis and postnatal growth.

PROSTATE MORPHOLOGY

In 1912, Lowsley studied the human fetal prostate and noted that the branching ductal system consisted of five distinct groups.[5] These lobes were termed the posterior, lateral (two), anterior, and middle lobes. The ducts of the posterior lobes originate from the floor of the prostatic urethra distal to the openings of the EDs and grow posteriorly. The epithelial buds of the two lateral lobes branch lateral to the verumontanum. The ducts of the middle lobe originate on the posterior urethra proximal to the openings to the EDs. The anterior lobe buds branch anterior to the verumontanum.

Xia et al. qualitatively examined prostate growth, histogenesis, and secretory activity in normal fetuses ranging in age from 20 weeks' gestation to 1 month (postnatal).[10] Sharply delineated "lobules" were not recognized. Two zones were identified, the inner submucosal zone (IZ) and

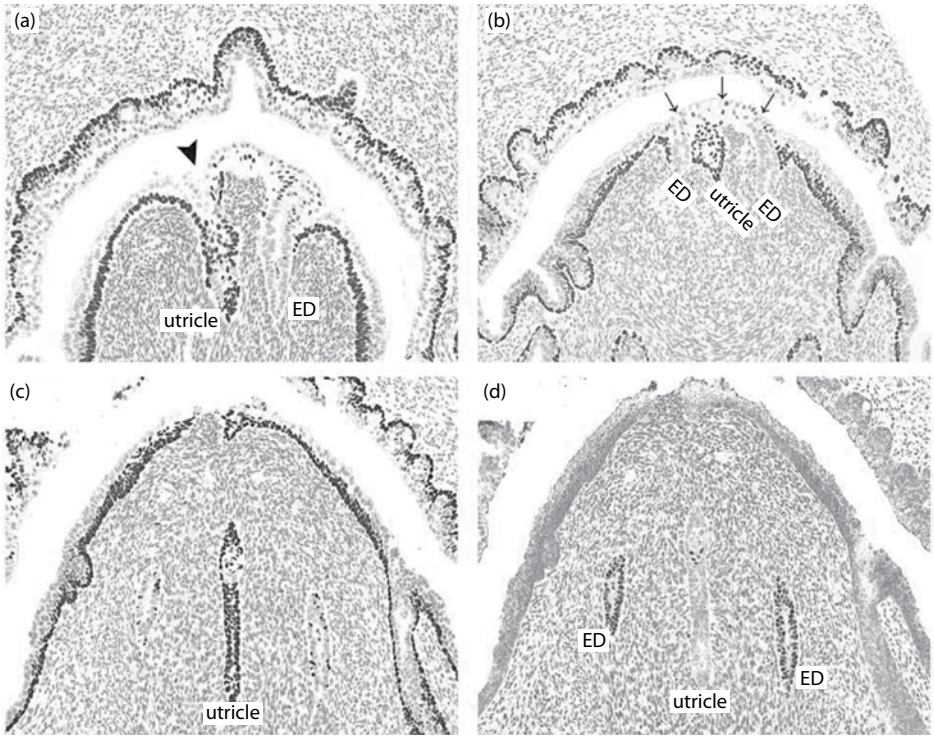

FIGURE 47.1 Cross section of human fetal prostate, age 15 weeks, demonstrates (a and b) two different specimens showing the evaginated p63 (basal cell marker)-positive cells that form the utricle (arrowhead) and only weakly staining basal cells in the UGS between the EDs (arrows), and that (c) the p63-positive cells of the utricle continue to grow into the midline of the mesenchyme and surround the small solid remnants of the MDs in its path, which (d) also express Pax-2 (marker for MDs and WDs). The EDs are also Pax-2 positive. ×200.

the peripheral zone (PZ). The IZ was characterized by a concentric mass of fibromuscular connective tissue (CT) containing ducts at various stages of development. The PZ contained less concentrically organized fibromuscular CT with secondary ducts, gland buds, and groups of acinar glands. Lowsley's work, together with Xia's observations, lends support to the current concept of the morphology of the adult prostate gland that exhibits three zones: central, transition, and peripheral zones, which correspond to three distinct sets of ducts. This is important since prostatic diseases are region specific, with prostate adenocarcinoma developing primarily in the PZ and benign prostatic hyperplasia (BPH) developing primarily in the transition zone. The development of BPH is important to understand since growth of new acini in this condition deviates from the normal development of most organs.[11] The prostate is the only organ that demonstrates new growth as part of the aging process. The new acinar architecture, though, is unlike that of the fetus since the ducts of the fetal prostate branch parallel and away from each other, rather than toward each other, as seen in BPH nodules.

ENDOCRINOLOGY OF PROSTATIC DEVELOPMENT

Development of the prostate is androgen dependent, and DHT is the active intracellular androgen.[3,12] The 5α-reductase deficiency syndrome is a form of autosomal recessive 46, XY Disorder of Sexual Development characterized by severe penoscrotal hypospadias, a blind vaginal pouch, and normal testes with normal epididymes, vasa deferentia, and seminal vesicles.[13] The EDs terminate in the blind-ending vagina, and the prostate is small or undetectable. The selective effects of testosterone and DHT are defined since the defect in virilization during embryogenesis is limited to the UGS and the anlagen of the external genitalia.

Although there is no compelling molecular evidence for homology between specific rodent prostatic lobes and human prostatic zones, the rodent has been extensively studied to further our understanding of prostatic development. Imperato-McGinley and coworkers demonstrated prostatic bud formation in the rat model of 5α-reductase deficiency.[14] This finding was unexpected since finasteride, a 5α-reductase inhibitor, did not completely abolish prostatic differentiation, which suggests that budding may have different thresholds of response for DHT. Further studies showed that flutamide, a nonsteroidal antiandrogen, in high enough doses to feminize the external genitalia of the male rat, failed to inhibit prostatic development, while cyproterone acetate (CA), a steroidal antiandrogen, inhibited prostatic bud development and external genitalia development. Low-dose DHT could induce prostatic buds in female fetuses. The WDs could not be abolished in males with CA, and high-dose antitestosterone treatment failed to inhibit prostatic buds. Although DHT is important for prostatic growth, the developing prostate may be responsive to exceedingly low levels of DHT or other androgens.[14]

Also, some aspects of postnatal prostatic growth may be independent of androgens, as castration in the rat during this period does not completely inhibit prostate development.[15,16] This suggests that other nonandrogen growth factors, such as peptide growth factors, are capable of mediating arborization and growth of prostatic ducts.[17] These findings suggest that varying phenotypes occur and are species dependent.

This concept is supported by the observations of Mahendroo and colleagues, where unexpected virilization in male mice lacking steroid 5α-reductase enzymes was observed.[18] These mice had normal external and internal genitalia and were fertile but had smaller prostates and seminal vesicles than controls. As expected, high testosterone levels were found in target tissues. DHT administration led to an increase in seminal vesicles and coagulating gland wet weights in the 5α-reductase type 2–deficient mouse and an increase in the prostate size, seminal vesicle, and coagulating gland in both the 5α-reductase type 1– and type 2–deficient mouse. When DHT was administered to the mouse deficient in only 5α-reductase type 2, no increase in prostatic size occurred, while DHT administered to the 5α-reductase type 1– and type 2–deficient mouse resulted in an increase in prostatic size. Androgen-dependent gene expression was decreased in the seminal vesicles lacking one or more of the 5α-reductase enzymes, but was restored with testosterone or DHT. These studies show that only testosterone is needed for differentiation of the male UGS in the mouse, and synthesis of DHT serves largely as a signal amplification mechanism.

Using immunohistochemistry, we studied human fetal prostates, gestational ages 7–22 weeks, and stained representative tissue sections with antibodies to the androgen receptor (AR) and 5α-reductase.[19] At 7 weeks, we demonstrated AR and 5α-reductase expression in the peripheral stroma, above the EDs, while only AR was seen in the UGS luminal epithelium. By 9 weeks, AR expression was ubiquitous in the stroma and suprabasal cells of the UGS but was observed in the basal cells of only the central dorsal UGS below the EDs. Stromal 5α-reductase expression was significantly increased and was observed throughout the UGS. By 11–13 weeks, AR expression increased in the stroma, especially in the periphery. Epithelial AR increased from the base to the apex, with AR observed in all cell layers of the UGS, ducts, and acini, except for the basal cells of the UGS and ducts above the EDs, which remained negative. 5α-Reductase expression was observed throughout the stroma except in the ventral SM, ventral periurethral stroma, and posterior periphery, where expression was diminished (Figure 47.2). Epithelial 5α-reductase expression increased from the base to the apex, with no expression in the ductal epithelium of the posterior lobe (Figure 47.3). The lateral lobes showed only distal duct and acini expression, while the ducts emanating from above the EDs expressed 5α-reductase throughout their epithelium. By 22 weeks, AR expression was ubiquitous, with the greatest staining in the epithelium and the posterior and posterolateral peripheral stroma, while 5α-reductase was almost undetectable.

We concluded that epithelial AR expression is significantly greater below the EDs than above the EDs at each gestational age up to 22 weeks, when no difference in the AR expression pattern is observed in the gland and 5α-reductase is almost absent.[19] In contrast, UGS and ductal epithelial 5α-reductase are expressed in a gradient fashion from the apex to the base or bladder neck. This suggests a regional reciprocal relationship between select areas of stromal and epithelial AR and 5α-reductase expression. This detailed localization study supports other investigations that have suggested that DHT serves largely as a hormonal signal amplification during prostate development.[18,19]

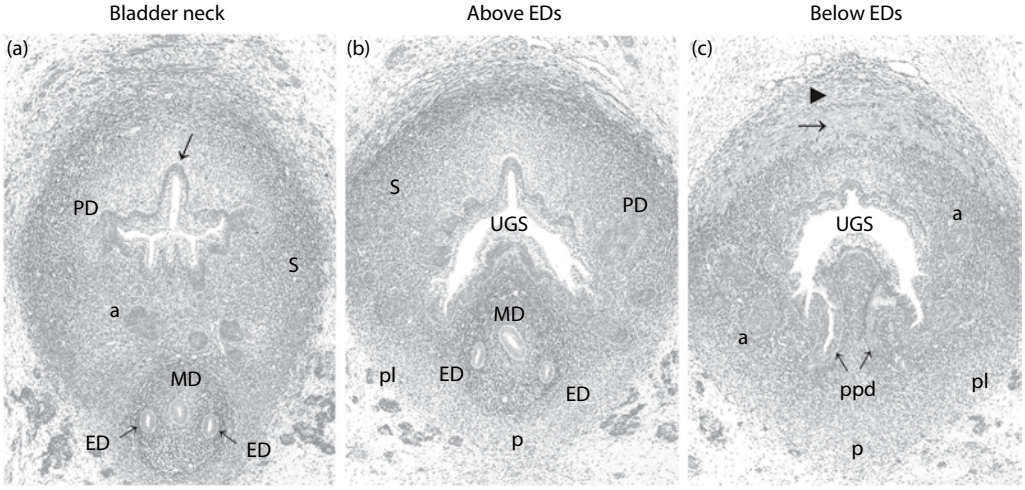

FIGURE 47.2 Cross section of human fetal prostate, age 11 weeks, showing (a) bladder neck region with significant 5α-reductase expression throughout the prostatic stroma and the central stroma surrounding the EDs and MDs. Expression is noted in the basal epithelium of the UGS (arrow) and in the prostatic ducts (PDs) and acini (a); (b) region between the bladder neck and the entrance of the EDs into the UGS with similar stromal 5α-reductase expression except posteriorly (p) and posterolaterally (pl), and much less UGS, prostatic ductal, and acinar expression; and (c) region below the entrance of the EDs into the UGS with no 5α-reductase expression in the UGS epithelium, posterior lobe ducts, or lateral acini. (There is no 5α-reductase expression in the posterior (p) and posterolateral (pl) stroma or in the SM (arrow) or SKM (arrowhead) in the anterior stroma. ×100; stroma (s), Posterior prostatic ducts, ppd.)

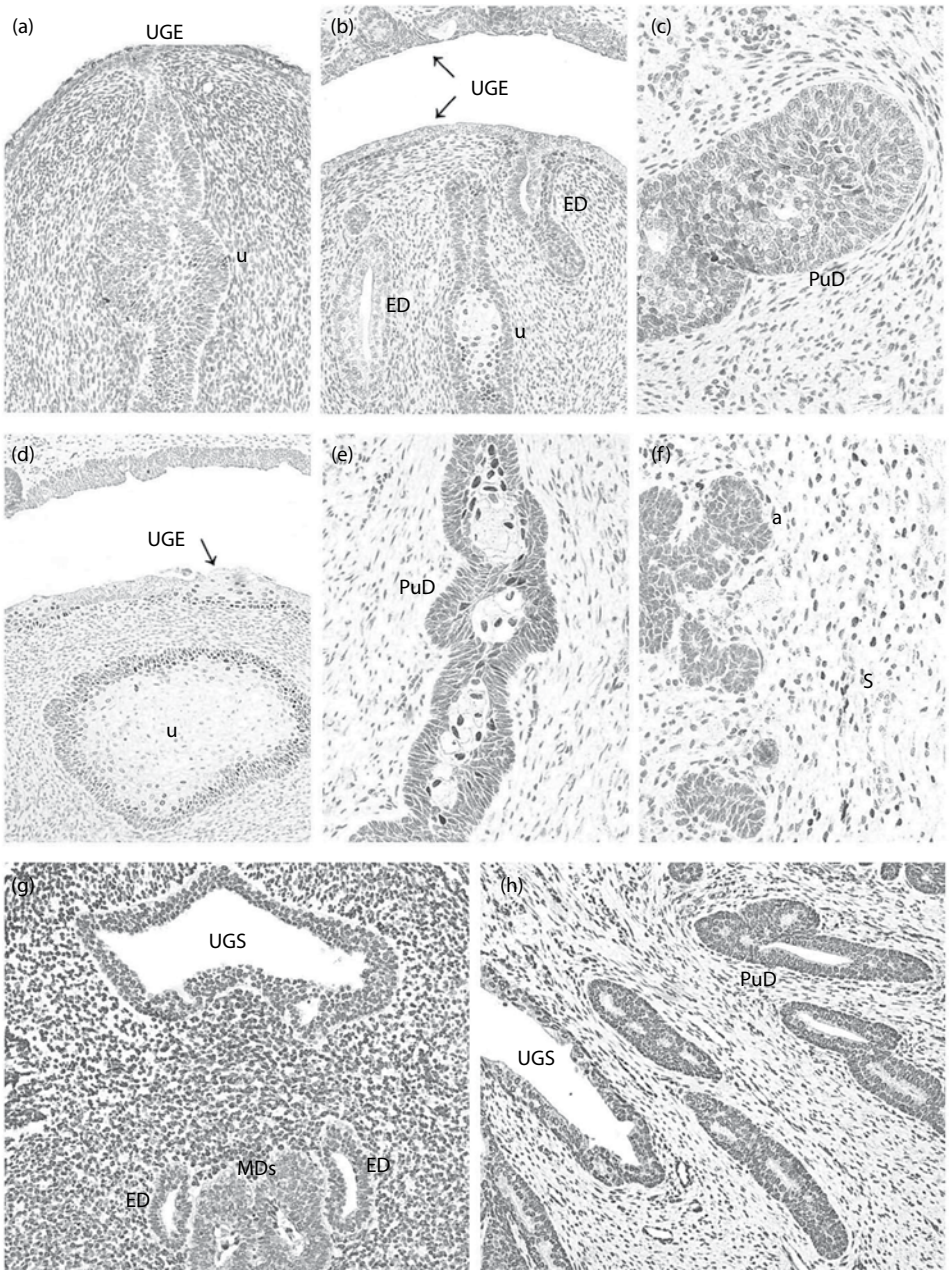

FIGURE 47.3 Cross section of human fetal prostate showing (a) ERα expression at 15 weeks in the ventral UGE and utricle (u) (×200); (b) ERα expression at 21 weeks in the UGE (arrows), utricle, and EDs (×200); (c) periurethral ducts (PuD) (×400); (d) ERα expression at 22 weeks in the UGE (arrows) and utricle (×200); (e) periurethral ducts (×400); (f) peripheral stroma with no staining of the acini (×400); and ERβ expression throughout the epithelium and stroma at (g) 7 weeks and (h) 24 weeks. ×200; stroma, s; peripheral acini, a.

There have been recent studies characterizing the prostatic stem cell or progenitor cells.[20–22] Using a murine model, Goto et al. identified two populations of cells in different regions of the prostatic ducts using an in vivo prostate reconstitution assay.[20] The first population had significant growth potential and was located in the proximal region of the ducts and in the urethra. The survival of these cells was androgen independent, and the cells were capable of regenerating prostatic tissue. The second population had less growth potential, was found in the intermediate and distal ductal regions, and was androgen dependent.

Wu et al. examined lymphoid enhancer-binding factor 1(LEF1), which is a major mediator and a target in the canonical Wnt/β-catenin pathway.[21] Canonical Wnt signaling is active during the development of the human fetal prostate. These investigators showed that LEF1 is expressed in the basal layer of the UGS by 8 weeks, prior to bud formation, while AR is expressed in the luminal cells. During prostate morphogenesis, LEF1 is expressed in the tips of the buds and the periphery of the solid ducts, but is not expressed in the stroma. This suggests a role in branching morphogenesis. In addition, using a murine model treated

with an AR inhibitor, Wnt/Lef1-positive basal progenitors were shown to repopulate the luminal compartment. In this model, Wnt/Lef1 activity identified an androgen-independent population of prostate progenitor cells. These observations also suggest that Wnt/Lef1 activity is important in organ maintenance and regeneration.

McNamara et al. recently studied the steroidogenic enzyme expression in the human fetal prostate.[22] Steroidogenic enzyme expression has been shown to be upregulated in a subset of castration-resistant prostate cancer.[23] They hypothesized that these enzymes are involved in de novo androgen synthesis. This study focused on the steroidogenic enzyme c17, which has two active sites. One site is 17-hydroxylase, which catalyzes the conversion of pregnenolone to 17-OH pregnenolone and progesterone to 17-OH progesterone. The second active site, 17,20 LYASE, catalyzes the next step in the conversion of testosterone 17-OH pregnenolone to dehydroepiandrosterone and 17-OH progesterone to Δ4-androstenedione. The expression of this marker, c17, in prostate cancer may identify more aggressive disease. These investigators showed significant c17 expression in both proximal ductal and acinar epithelial cells and some stromal cells of all the fetal prostates examined between gestational weeks 8 and 22. This suggests that c17 is expressed in a subset of progenitor cells, and that prostate cancer cells with similar expression have a more primitive, potentially more aggressive, subpopulation.[22] The expression of this marker, c17, in prostate cancer may identify more aggressive disease. These findings and the findings of other investigators have translational implications for the elucidation of the biology of both benign and malignant proliferative prostatic diseases.

STROMAL–EPITHELIAL INTERACTIONS

Stromal and epithelial interactions that occur in the developing prostate are androgen dependent.[15] Lasnitzki et al. performed tissue recombinant experiments by combining mesenchyme isolated from fetal rat or mouse UGS with fragments of prostate or bladder epithelium.[24] These tissue recombinants are grafted under the renal capsule of recipient animals and form prostatic ductal tissue. Cunha and Lung have utilized testicular feminization syndrome (*Tfm*) mice to elucidate the roles of epithelial versus mesenchymal AR in prostatic development.[25] *Tfm* results in complete failure of the prostate to develop due to defective or absent AR. The WDs undergo degeneration, and the external genitalia are feminized despite normal testosterone levels. Therefore, *Tfm* mice have deficient AR and fail to develop prostates. When tissue recombinants constructed of wild-type mesenchyme and *Tfm* epithelium are exposed to androgen as a result of grafting of the recombinants into intact male hosts, normal prostatic morphogenesis ensues.[24–26] When the *Tfm* mesenchyme is combined with either the *Tfm* or the wild-type epithelium, the prostate does not form. From these studies, they concluded that there is a critical role for mesenchymal AR in prostate development, and that many androgen effects on prostatic epithelium do not require epithelial AR but are elicited by the paracrine action of AR+ mesenchyme. It is interesting to note, though, that mouse prostatic epithelial ARs are not expressed until postnatal day 1, while human prostatic epithelial ARs are present in the urogenital epithelium (UGE) as early as 7 weeks' gestational age.[19,27,28] Prostatic epithelial ARs are required for the expression of AR-dependent secretory proteins during postnatal development.

Allgeier et al. examined the androgenic regulation of ventral epithelial bud number and pattern in mouse UGS.[29] Control mice are known to have two rows of three or four prostatic buds at birth conform to a relatively sharp bimodal distribution on the left–right axis. The mechanism underlying androgen regulation of ventral bud number and patterning is unknown. Using UGS from *Tfm* males and flutamide (antiandrogen)-treated mice, these investigators showed initiation of small ventral buds, which suggests that this process, in mice, may be androgen independent. Surprisingly, DHT treatment of *Tfm* males significantly increased the expected number of ventral buds per UGS in *Tfm* males, and the distribution of the buds appeared to be broadly bimodal. These studies demonstrate that UGSs from *Tfm* males are androgen responsive. These results also suggest that ventral UGS bud number responds biphasically to androgen stimulation.[29] Baseline number is defined when androgens are at baseline or very low, with increased androgenic stimulation leading to an increased number of ventral buds. Nonetheless, additional androgenic stimulation leads to a reduced ventral bud number to the baseline.

Tissue recombinant experiments have also been used to examine epithelial–mesenchymal interactions on the differentiation and organization of prostatic smooth muscle (SM).[30] Experiments combined adult prostatic epithelium with UGM or seminal vesicle mesenchyme (SVM), or bladder epithelium with UGM or SVM. Prostatic ducts developed in all tissue recombinants when UGM was used with either epithelium. SM cells also organized into sheets resembling prostate. When SVM was combined with either epithelium, the prostatic ducts were surrounded by thick SM cells resembling seminal vesicle. The SM was unorganized in grafts of SVM or UGM. These experiments suggest that male UGM dictates spatial organization, but SM differentiation is induced by epithelium. Urothelium may also direct the organization of SM tissue, since urothelium is thought to be a potent inducer of SM differentiation. Cunha et al. have shown that the proximal segments of prostatic ducts near the urethra express urothelial membrane antigen and have associated thick layers of SM cells surrounding them.[12]

All these tissue recombinant experiments show that interactions between the mesenchyme and epithelium are reciprocal.

HORMONAL IMPRINTING

For more than half a century, the role of natural and synthetic estrogens in prostate development and the effects of hormonal imprinting have been studied.[31–33] Estrogens alter the hypothalamic pituitary gonadal axis, resulting in decreased androgen levels and subsequent regression of the prostatic epithelium.[34,35] Investigations have focused

on the correlation between estradiol and prostatic development in fetal mice, depending on their intrauterine position; the effects of experimental increases in estradiol in mouse fetuses; the inhibition of prostate development following administration of high-dose estrogens; and the opposing effects of high- and low-dose estrogen on prostatic development.[36]

It has been postulated in humans that the early testosterone surge at 30–60 days of life may be a critically important "imprinting" event that may have an impact on the gland's propensity for future abnormal prostatic growth and disease. Hormonal imprinting has been studied in the rat.[37] Naslund and Coffey showed that early hormonal surges are requisite for normal adult prostate growth in the rat, and that an alteration in the normal endocrine events that occur shortly after birth can have significant and permanent effects on the androgen sensitivity and growth of the adult prostate.[38] These hormonal surges are thought to affect prostatic growth by altering the properties of the prostatic stem cells. Recently, Tsujimura et al. have shown that the proximal region of the mouse prostatic ducts is enriched in a subpopulation of epithelial cells that have a number of properties of stem cells: they are slow cycling, they possess high in vitro proliferative potential, and single cells are able to reconstitute complex highly branched glandular structures in vitro that contain basal and luminal cells.[39] The absolute number of these stem cells is important because it ultimately determines the size of the gland. Therefore, hormonal events occurring before puberty can imprint or program the prostatic size, androgen sensitivity, and function and maintenance of the stem cells.

Prins and others have shown that brief exposure of rodents to estrogens during the neonatal period leads to permanent irreversible and dose-dependent effects on the prostate gland's morphology, cellular organization, and function.[2,3,40,41] If estrogenic exposure is high, the permanent imprints include reduced prostatic growth, epithelial differentiation defects, altered secretory function, and aging-associated dysplasia similar to prostatic intraepithelial neoplasia (PIN). This process, referred to as estrogenic imprinting or developmental estrogenization, is used as a model to evaluate the role of exogenous and endogenous estrogens as a potential predisposing factor for prostate diseases later in life.[40,41]

Prins's study also examined the effects of neonatal estrogen exposure on the development of the AR.[41,42] Estrogen receptors (ERs) have been shown to be strongly expressed in the mouse prostate mesenchyme.[43] While the stroma is strongly ER+, the prostate SM is weakly to negatively stained after differentiating from mesenchyme. Fibroblasts remain strongly ER+. There are no ERs in the epithelium of the prostate. Brief exposure to neonatal estrogen downregulates AR and permanently alters its expression, as well as retards ductal development.[41,42] SM development is generally unaffected, as is the development of basal cells. Estrogenization does not inhibit epithelial cell differentiation (determined by the appearance of luminal cell cytokeratins) completely, indicating that initiation of cytodifferentiation precedes elevated AR expression rather than increasing AR, triggering cytodifferentiation. These experiments suggest that functional differentiation is dependent on AR expression in epithelial cells.

Although this response is mediated through alterations in steroid receptor expression, other downstream mechanisms in the signaling cascade that mediate prostate ductal morphogenesis may be involved. The Sonic hedgehog (*Shh*) gene encodes a secreted glycoprotein that is expressed at many sites in the vertebrate embryo and participates in the molecular signaling for the development of the notochord, limb, hindgut, and genitourinary tract.[44,45] Loss of *Shh* function results in severe defects in neural and skeletal development, growth inhibition, and embryonic lethality. Using a murine model, *Shh* is expressed in the prostatic anlage of the UGS, and that expression is stimulated by testosterone. Pu et al. show that highly localized *Shh*-patched *gli* expression, along with regulation of downstream morphogens, participates in dichotomous branching during prostate morphogenesis.[45] Neonatal exposure to high-dose estadiol suppressed *Shh*-patched *gli* and blocked ductal branching in the dorsal and lateral prostate lobes.

Barnett et al. studied *Shh* expression in the human fetal prostate ages 9.5–20 weeks' gestation.[46] *Shh* expression was present in the prostatic urothelium, prostatic ducts, and glandular epithelium at 9.5, 11.5, 13, and 16 weeks and in the prostatic buds by 11.5 weeks. Staining was observed in the EDs, MDs, and anterior SM and skeletal muscle (SKM). Staining intensity diminished after 16 weeks, as testosterone levels declined to baseline, and was almost absent by 18 and 20 weeks, suggesting a direct relationship between testosterone levels and *Shh* expression.

Other studies of the effects of estrogen on the prostate have used the induction of squamous metaplasia (SQM) as a reliable marker for estrogen action on the gland.[35,47] Risbridger et al. studied this transformation of the epithelium and showed proliferation of basal cells and the expression of K10.[35] They also showed that mice lacking the stroma and/or epithelial ERα did not develop SQM.[35] These studies suggest that stroma and epithelial ERα are required for the induction of SQM in the prostate gland.

Shapiro et al. examined the immunolocalization of ERα and ERβ in the human fetal prostate (Figure 47.3). ERα expression was not detected until 15 weeks, with sparse staining in the utricle.[48] By 19 weeks, increased ERα expression was seen within luminal cells of the ventral UGE, basal cells of the dorsal UGE, the utricle, distal periurethral ducts, peripheral stroma, and the posterior prostatic duct. K14 is detected in the basal cells of the UGE and in several posterior acini. At 22 weeks, ERα expression is more intense in all these areas. ERβ is expressed throughout the UGE, EDs, MDs, and entire stroma at 7 weeks. Intense ERβ staining is observed in these areas and the prostatic buds by 8 weeks, with persistent intense staining through 22 weeks. The work of Shapiro and associates shows the earliest expression of ERα (15 weeks) and ERβ (7 weeks), and that the induction of SQM in the UGE, distal periurethral ducts, and utricle is associated with ERα expression in these areas, while the induction of SQM in peripheral prostatic acini is associated with peripheral stromal ERα expression. This suggests important estrogen signaling pathways in the human fetal prostate via ERα that involve epithelial–epithelial and epithelial–stromal interactions. Also, the timing of the appearance of SQM is thought to be associated with the decline in testosterone

levels after 18 weeks, when the Leydig cells are known to regress.[49] This results in an imbalance of the hormone milieu with a predominance of estrogens, which may then induce metaplastic changes.

The role of ERα and ERβ in prostatic development has been further elucidated in studies of the estrogen receptor α knockout (ERKOα) and estrogen receptor β knockout (ERKOβ) mouse, respectively.[50,51] Couse and Korach studied neonatal diethylstilbestrol (DES) exposure in males using both ERKOα and ERKOβ knockout cell lines.[51] The ERKOα males were completely resistant to the effects of neonatal DES exposure, and the ERKOβ response was similar to that of the wild type, with significant decreases in the AR levels and seminal vesicle size, increased stromal mass, marked epithelial hyperplasia and dyplasia, and lymphocytic infiltration. They conclude that the initial effect of DES resulting in the downregulation of AR levels is mediated by ERα. Therefore, the ERKOα males did not show any of the effects of neonatal DES, but unlike the wild type, the AR levels recover in the adult ERKOβ males.

Other investigators suggest an association of ERβ in the pathogenesis of prostate cancer since ERβ expression is downregulated in prostate cancer, supporting its role in prostatic cellular homeostasis.[52] We show that ERβ expression is intense during the early period of prostatic ductal morphogenesis and may be critical in maintaining normal glandular growth and proliferation.

Hofkamp et al. studied the effects of murine fetal exposure to estrogenic ultraviolet filters found in sunscreen and cosmetics.[53] They showed that fetal exposure to 4-methylbenzylidene camphor (4-MBC), which binds to ERβ in vitro but binds to ERα in vivo, resulted in a significant increase in tissue volume in the prostate and accessory sex glands. In the caudal region of the dorsal prostate ducts, there was a significant increase in volume due to an increased number of ducts budding from the UGS. This finding was in contrast to the increased ductal volume of the ventral prostate that resulted from increased branching morphogenesis, resulting in an increase in distal tip volume. These studies show that environmental endocrine disruptors alter normal prostate development.

Taylor et al. reviewed the mechanisms for the effects of estrogenic environmental chemicals and drugs on the developing male urogenital system.[54] There is now evidence that estrogens at very low concentrations during the early stages of prostate development can stimulate both fetal and neonatal prostate growth and lead to prostate disease in adulthood. Bisphenol A (BPA) is an environmental endocrine-disrupting chemical found in plastics, epoxy linings of food and beverage cans, and numerous common household products that bind to both the ER receptor subtypes and AR.[55] BPA is of great interest since it can be detected in >90% of people. In a fetal mouse model of UGS mesenchymal cells in culture, BPA disrupts prostate development by stimulating the expression of several genes involved in epithelial proliferation and inhibiting genes involved in apoptosis. The treatment with BPA or estradiol affected genes with cellular functions relevant to steroid hormone signaling and metabolism and to inter- and intracellular communications that promote cell growth. It is then easily conceivable that BPA is capable of disrupting the development of the entire male reproductive tract in the mouse. Since the "plastic revolution" began in the 1970s, males exposed to significant levels of environmental chemicals are just starting to approach the age where prostate disease would be expected to occur.[54,55] A comprehensive review by Hu et al. describes the effect of lifelong reprogramming by possible epigenomic alterations in human prostate stem or progenitor cells due to developmental estrogenization or transient adult exposure.[56] Recent studies indicate that these stem cells and early-stage progenitor cells may be direct carcinogenic targets and the cell of origin for the initiation and promotion of malignant prostate diseases in aging men.[56,57]

PROSTATE MORPHOMETRY

Shapiro et al. developed a technique for quantifying the cellular elements of the prostate that involves double immunoenzymatic staining and computer-assisted color image analysis.[58,59] The only comprehensive study of prostatic morphometry in the prepubertal male has been reported by Shapiro et al.[60] Quantitative morphometric studies were performed on pediatric and other nonhyperplastic prostate specimens obtained from 45 males ranging in age from 2 days to 40 years. The entire group was stratified based on age into categories reflecting the neonatal, childhood, peripubertal, adolescent, and young adult periods. Double immunoenzymatic staining using antiactin and anti-prostate specific alkaline phosphatase (PSAP) was used to label the tissue components.[59] Color image analysis demonstrated age-related changes in the density of SM that appear to parallel serum testosterone levels that vary due to the postnatal testosterone surge and the rise in testosterone at the onset of puberty.[3,61]

A progressive decrease in SM area density throughout childhood, prepuberty, and puberty was observed. The density of SM significantly increased following puberty and throughout adolescence and early adulthood. There was a concomitant increase in CT from the neonatal period throughout childhood, prepuberty, and puberty and a decrease after puberty and throughout adolescence and early adulthood. Since the changes in SM and CT were inversely related, the percent contribution of the stromal compartment to the total gland remained constant. No significant changes were seen in the epithelium or glandular lumen during these periods. The stromal-to-epithelial ratio remains constant from birth to age 40 in nonhyperplastic glands and is similar to those in asymptomatic and symptomatic BPH tissues. These morphometric observations suggest that BPH is not a unique stromal process.[60] These studies demonstrate that the stromal compartment is a dynamic structure, and the relationship between changes in cellular content and hormone milieu may be important to our understanding of growth of the prostate from birth to age 40 and the subsequent development of BPH.

Shapiro et al. compared prostate development in normal human male fetuses and those with myelomeningocele (MMC) at 20 weeks' gestational age.[61] Immunohistochemical staining was performed using Masson's trichrome and antibodies to SM and SKM actin. S-100 protein for Schwann cell localization and neurofilament protein was also performed. These studies

demonstrated a marked decrease in the peripheral innervation to the prostate in MMC. Trichrome and SM actin staining also showed that SM in MMC specimens was less well differentiated. Prostatic size, ductal morphogenesis, and SM were decreased when compared with controls. At the level where the EDs enter into the prostatic urethra, the mean cross-sectional area was 6.79 and 11.91 mm^2 in the MMC and normal prostate, respectively. Control prostates showed posterior peripheral SM surrounding acini, which subsequently become cannulated, as well as SM surrounding the EDs and along the periphery. In MMC prostates, SM was absent in the periphery where ductal branching and formation of acini normally occur. The other areas of SM were also poorly formed. They concluded that there is a global defect in the development of SM in MMC prostate at 20 weeks' gestation. Since the peripheral nerve density was diminished in the MMC prostate, an intact nervous system may be important in the SM and ductal morphogenesis of the developing prostate.

SUMMARY

The foundation for our understanding of the development of the human prostate was derived from human fetal studies reported by Lowsley and by unraveling the biochemical basis for the 5α-reductase deficiency syndrome. Tissue recombinant studies, genetic knockout studies in nude mice, and meticulous step sectioning of fetal prostates with immunohistochemical staining gestation have greatly enhanced our understanding of prostatic development. Future studies in novel animal models will provide important insights into the mechanisms of altered endocrine signaling pathways due to exposure to endocrine-disrupting chemicals. These altered pathways in prostate development lead to lifelong reprogramming of prostatic structure and gene expression, which may predispose aging men to the development of malignant prostate disease.

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CHAPTER 48

Basic Science of the Urinary Bladder

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INTRODUCTION

Although the urinary bladder is an outwardly simple hollow organ, it is unique. No other organ is evolutionarily programmed to fill with fluid over hours at low pressures and then contract on demand to evacuate its contents. The bladder is the only autonomically innervated organ under voluntary control. Indeed, the sociobiologic etiology and reasons for the existence of this unique behavior have been argued for decades. Although the ability to accommodate a fluid volume is thought to largely represent a passive phenomenon, this is not the case. Recruitment of active neuromechanical properties is crucial for the maintenance of low intravesical pressures during filling, and to this end, the character of the surrounding cellular and extracellular matrix (ECM) elements can either facilitate or compromise this function. It demonstrates a remarkable integration of neuromuscular, mechanical, and physical properties that are crucial for its normal function. Bladder contraction (emptying), on the other hand, is largely an active neuromuscular process, although it is also influenced by the physicochemical nature of the ECM and obviously depends on the overall mass and optimal functional status of bladder smooth muscle cells (bSMCs). Underlying the homeostasis of the bladder is cell biology governed by appropriate cell signaling in response to the mechanical and structural environment. These signaling responses to the environmental cues lead to maintenance or changes in gene expression and cellular function. This chapter reviews some of the biologic concepts related to normal bladder development and function, a complex orchestration of events that, if disturbed, can lead to a significant functional disharmony that places both continence and renal function at risk.

BLADDER DEVELOPMENT

The urogenital sinus develops from the dividing cloaca to form the bulk of the urinary bladder, with its endoderm giving rise to the urothelium, and the surrounding mesenchyme to the lamina propria, submucosa, smooth muscle layer, and adventitia. A smaller and albeit crucial part of this organ—the trigone—originates from a combination of bladder and ureteric muscle and, in a recent study, endoderm.[1–3] Specific signals are required for the cellular orchestration to proceed. For example, BMP7 and c-Jun N-terminal kinase (JNK) are required for the apical–basal direction of endodermal cell division, leading to cloacal septation.[4] Also, retinoic acid signaling in the urogenital sinus is required for a fully formed urinary bladder, although the caudal portion of the sinus will still form a normal urethra without retinoic acid. Cloacal and bladder expansion is accompanied by an increase in the volume of mesonephric urine, an ultrafiltrate containing growth factors similar to serum,[5,6] which provides the first mechanical cues (pressure and strain) through the increasing volumes to the cloaca and primitive bladder[7] as the vesicoallantoic canal closes off to form the median umbilical ligament. In males, the caudal portion of the urogenital sinus contributes to the valve system.

The initial formation of the vesicoureteric junction (VUJ) in the bladder begins with the nephric ducts and then the relocalization of the ureteric ducts by intercalation of fingerlike protrusions of ureteric cells into the caudal aspect of the bladder wall.[8–11] After the ureter joins the bladder, the common nephric duct regresses through an ill-defined process, which differs in females and males. In the *sal1* model, the lack of remodeling of the common nephric duct is associated with posterior urethral valves (PUVs). As such, malformation of the VUJ appears to have a gender-specific and heterogeneous genetic basis in humans.[12–19] A more caudal ingrowth of the initial mesonephric ducts leads to altered localization of the ureters.[20,21] In animal models, the expression and activation of a variety of molecules, including LAR family kinases,[22] *raldh2*, *gata3*,[23–25] *pax2*, *emx2*,[26] urothelial uroplakin IIIa, and ureter-specific *robo2*, are required for proper incorporation of the ureters into the trigone and formation of the VUJ.[9,13,27]

It is not completely clear how neuronal cells develop in the bladder, although in other tissues neurons develop alongside the vasculature or differentiate from mesenchyme (e.g., in the gut). However, neurotrophic factors (NGF, NTs 3–5, and BDNF) increase in a spatiotemporally controlled fashion from prenatal to postnatal periods, when neural reflex pathways are reorganized.[28,29] Another less defined region of the bladder, the adventitia or serosa, is composed mainly of fibroblasts, which are more numerous in exstrophied bladders. It is not clear whether the serosa is more specialized than adventitial layers in other organs, but serosal fibroblasts do play a role in experimental obstruction.

Early in gestation, the undifferentiated bladder mesenchymal cells are highly proliferative[30] and strongly

express genes relevant to retinoic acid or ephrin signaling, cell cycle genes, and midkine.[31] Through spatiotemporal interactions with the surrounding primitive urothelium and hedgehog signaling,[32,33] differentiation begins. Bladder mesenchyme expression patterns shift toward genes involved in differentiation of smooth muscle cell markers that will come to signify their smooth muscle lineage—including α- and γ-smooth muscle actin, desmin, and smooth muscle myosin[34]—in a process that coincides with changes in expression of specific ECM proteins, such as collagen, fibronectin, and laminin.[35] Particular molecules in the urothelium, including *shh* and *p63*, have been identified that are critical for normal bladder muscle development,[33,36] through their regulation of smooth muscle regulatory factors, e.g., *msx*.[37] Mutations or alterations in the expression of the above pathways and desmoplakin-related genes have been identified in cases of bladder exstrophy.[38–40] The early specific epithelial–mesenchymal–ECM interactions among the different developing cell types and their surrounding environment are critical for orderly differentiation and development. For example, collagen type IV, laminins, and fibronectin have been found in the basal lamina during development and are probably important in mediating interactions and forming a barrier between the developing urothelium and its underlying mesenchyme.[3]

Other ECM molecules, such as the structural collagens, are expressed differently between the lamina propria and the detrusor muscle fibers,[41] and interact with adjacent cells via specific cell surface receptors, the most important of which are believed to be the integrins.[42] The cell–matrix transduction of different stimuli through different mechanoreceptors (integrins, cell adhesion molecules, and selectins) regulates cellular proliferation and differentiation, as well as modulates ECM synthesis.[42] Consequently, normal prenatal bladder development not only results from a complex interaction of ECM and developing cells but also depends on appropriate mechanical stimulation. As gestation progresses, ECM cellular interactions vary with the multiple factors regulating the mechanical distension stimulus. Compliance appears to increase gradually,[43] as the bladder wall thickness and composition change,[44] with appropriate innervation that responds to increased demands of micturition as the fetus grows. Later, the bladder acquires a pattern of cyclical emptying.

CONTRACTION AND RELAXATION

As storage and emptying alternate, the complex function of the detrusor muscle demands integrated control of perhaps its most important cellular component, the smooth muscle cell. During filling, bSMCs must relax and elongate over a considerable length of time (hours) to accommodate the urine volume at low pressures. Under normal low-pressure filling conditions, the bladder will expand and unfold its matrix[45] and cells, leading to increased anisotropy in particular regions of the bladder.[46,47] Conversely, during micturition a rapid change occurs, leading to coordinated and synchronized force generation and cell shortening. By means of dense innervation and abundant intercellular communications (gap junctions), these activities—contraction and relaxation—respond to various transmitters and modulators that activate different cellular pathways.[48]

Contraction of bSMCs is mainly the result of interaction between the contractile proteins, actin and myosin, in a manner similar to that of other muscle cells in the body. In an energy-dependent process, a multistep enzymatic reaction allows for the cross-bridging and attachment of these two proteins in a cyclical fashion, following the same general scheme proposed for skeletal muscle. ATP is the immediate energy substrate, and is crucial for membrane pump Ca^{2+} handling, phosphorylation events, and cross-bridge cycling. The cellular concentration of ATP is therefore essential, and is maintained by mitochondrial respiration, glycolysis, and conversion of the high-energy compound phosphocreatine. Regulation of free Ca^{2+} in the cytosol is a highly energy-dependent process. Activation of the contractile apparatus by myosin light-chain kinase is modulated by cytosolic Ca^{2+}, whose concentration is regulated by Ca^{2+} channel pumps in the sarcoplasmic reticulum and plasma membrane. Furthermore, relaxation of smooth muscle involves restoration of the membrane gradients via β3 adrenergic receptor stimulation and downstream opening of the several potassium (K^+) channels, including BK channels.[49,50] Significant energy expenditures are required to maintain these Ca^{2+} gradients. Therefore, mitochondrial function is yet another factor essential for the normal generation of the contractile force by bSMCs.

Even though different isoforms have been described for both actin and myosin, the functional significance of the isoforms and their differential regulation remains unclear. Smooth muscle myosin is composed of a pair of heavy chains and two pairs of light chains. Through alternative splicing, vertebrate smooth muscle myosin heavy chains can be expressed in two C-terminal isoforms (SM1 and SM2) and two N-terminal isoforms (SMA and SMB). Some studies suggest that the SM1 isoform creates better contractile filaments than SM2, and that SMB is associated with increased ATPase activity, increased shortening velocity, and more phasic contractions than the SMA isoform.[51–53] Although it remains possible that the presence and relative concentrations of actin and myosin vary with developmental state and in response to obstruction or other pathologic processes,[53–56] their function not only supports the contractile apparatus but also helps to define the cytoskeleton. Indeed, the cytoskeletal framework of the bSMCs forms a dynamic structure, with linkages to the ECM. At the same time, these points of linkage, or adhesion complexes with the ECM, mediate intracellular signaling that leads to gene expression, cell migration, cell growth, apoptosis, and adaptation.[48,57,58] Although a relatively novel finding in urology, this paradigm has been appreciated in other biologic systems where it governs cell–matrix relationships in multiple ways.[59]

MECHANOTRANSDUCTION

Cycling between filling and emptying continually exposes the bladder to homeostatic levels of mechanical stimulation, with force transduction to the cells and their surrounding environment. Homeostatic levels of mechanical

stimulation in the bladder allow for maintenance of cellular phenotype, while defunctionalization (such as bilateral ectopia and urinary diversion) leads to decreased detrusor growth.[60] As a conditioning and modifying process, forcible changes in cell shape induced by various combinations of stretching, contraction, pressure, and membrane and cytoskeletal deformation eventually lead to alterations in gene expression (Figure 48.1). The macroscopic changes often appreciated in the bladder wall are thus the result of transcriptionally mediated tissue remodeling and activation of different molecular pathways. The process of converting physical forces to biochemical signals and integrating these signals into a cellular response (e.g., transcription or movement, e.g., contraction) is known as mechanotransduction.[61] It is an important concept in bladder development, homeostasis, and the bladder's response to different pathologic stimuli. Critical to this process is the signaling system mediating mechanotransduction, which can lead to both short- and long-term changes in gene transcription and cell behavior, involving feedback loops to regulate the responses. In disease, the intensity, duration, and feedback of the mechanotransduction responses may become dysregulated.

Some of the earliest-described mechanoresponsive molecules involved in the bladder's response to distension were prostacyclins.[63] The production of prostacyclins was later found to occur through mitogen-activated protein kinase (MAPK)–induced cyclooxygenase 2 (COX-2) activity.[64] Depending on the particular species of prostanoid produced, prostacyclins activate signaling pathways, and affect muscarinic responses and bladder contractility[65–67] either directly or through cross talk with the urothelium.[68] The bladder, among other mechanosensitive organs, derives mitogenic stimuli from mechanical stimulation through the activation of members of the MAPK family—the JNK,[69,70] p38 MAPK,[71] and extracellular signal-regulated kinase (ERK)[72]—as well as phosphoinositide 3-kinase (PI3K)/AKT,[73,74] STAT3,[75,76] calcineurin,[77–79] NFATc,[80] β-catenin,[81] and mTOR.[82] Through these pathways, signals are transmitted to activate various transcription factors responsible for cell growth, hypertrophy, and survival. Less studied are the mechanosensitive pathways that may be important for cellular differentiation. It has, however, been noted that the duration, cyclicity, and matrix context of mechanical strain are critical for the mitogenic signaling to occur in bladder smooth muscle, as well as other tissues[72,83,84] (for a review, see Aitken and Bagli[85,86]). It is probable that the pathways are multiple and perhaps redundant; however, it is currently believed that integrins play an important role in these series of

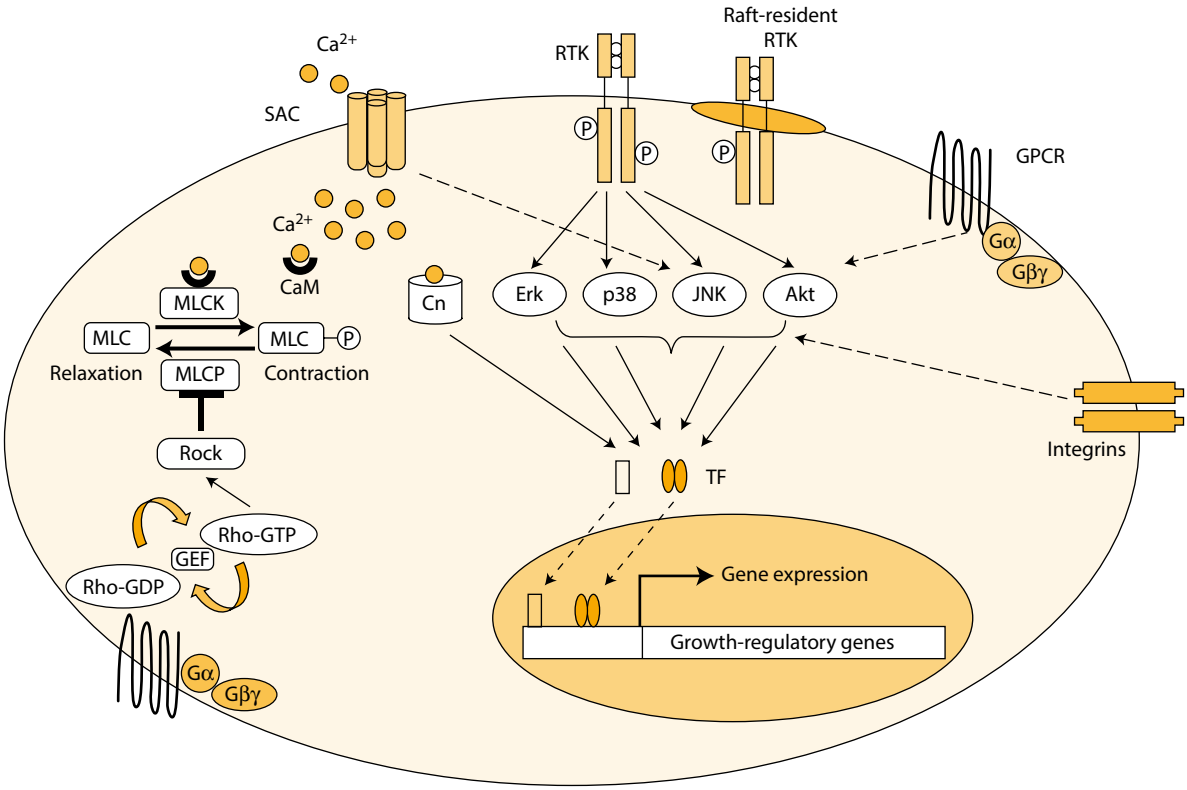

FIGURE 48.1 Signaling cascades in bSMCs: external stimuli are transduced by SACs, receptor tyrosine kinases (RTK), G-protein-coupled receptors (GPCR), and integrin subunits. SAC-mediated calcium (Ca^{2+}) entry promotes calmodulin (CaM) binding and activation of myosin light-chain kinase (MLCK), leading to MLC phosphorylation and initiation of smooth muscle contraction. MLC phosphatase (MLCP)–induced relaxation is inhibited by Rho-associated kinase (ROCK). Ca^{2+} influx also activates calcineurin (Cn), leading to dephosphorylation and nuclear translocation of transcription factors (TF). RTK activation promotes activation of the MAPKs Erk, p38 stress-activated protein kinase 2 (SAPK2), JNK, and Akt. These signaling intermediates in turn promote activation and nuclear translocation of TF, and alterations in gene expression. (Adapted from Adam, RM. *Nephron Exp Nephrol* 2006;102:e1–7. With permission.)

events.[87] These linkage molecules are almost ubiquitous, acting as a relay between the matrix and different cells. Individual tissues thus display different complex responses to mechanical stimulation, the eventual response modulated by the type of mechanical stimulation, as well as by the signaling molecules and transcription factors expressed by that particular tissue.[61] As a group, these ECM receptor molecules provide a physical link between cell membranes and surrounding structural ECM proteins, such as collagen, laminins, vitronectin, and fibronectin. In particular, the integrins represent a large and versatile family of heterodimeric transmembrane mechanoreceptors capable of transducing a wide range of alterations in the cell microenvironment.[88] Growth factors can further stimulate cell responses through integrins by either mutual interaction, or integrin clustering with growth factor receptors. This process is tightly regulated through expression of different integrin subunits specifically modulated by different growth factors and/or ECM molecules under different developmental and pathologic situations. Even though much of the current knowledge about these molecules remains to be revealed in relation to the bladder, their importance in response to bladder distension and dynamic alterations in ECM expression has been demonstrated.[42]

Integration of mechanotransduction to the cytoskeletal machinery occurs through several mechanisms. Homeostatic levels of distension activate muscarinic responses through PI3K and rho kinase, leading to activation of myosin light-chain kinase. Finally, mechanotransduction in bladder muscle also occurs through stretch-activated ion channels (SACs), which respond to strain by increasing intracellular calcium (Figure 48.1).[87] This is regulated in part by β3-adrenergic signaling, which activates large-conductance BK channels, and by other K^+ channels to restore the resting membrane potential and return smooth muscle cells to a relaxed state.[49,89–91]

Distension of the bladder may affect other cell types as well. Working with this hypothesis, several studies have examined the participation of urothelial-, submucosal-, and interstitial-type cells in mechanotransduction. The proximity of basal urothelial cells to afferent neurons makes their responses to mechanical stimulation potentially important for neuronal responses. For instance, COX-2 expression via PKCζ activity is increased through mechanical stimulation of urothelial cells.[92] Another way that the urothelium contributes to the integration of mechanical stimuli is through stretch- and pressure-induced activation of the muscarinic, purinergic, nitric oxide, calcium, and vanilloid channels, the latter providing a possible link between mechanical strain to pain or inflammatory pathways of the bladder.[93,94] In addition to urothelial cells, other cell types may play a neuromodulatory role, e.g., interstitial cells of Cajal,[95–99] $PDGFRa^+$ cells,[100] and suburothelial cells.[101] Mechanical stimulation of stromal cells with urothelial cells can propagate formation of a full-thickness differentiated urothelium with complete barrier function.[102,103] This is likely through the stimulation of the stroma to produce the fibroblast growth factor and nerve growth factor, as the urothelium itself is not known to proliferate in response to cyclic stretching.

SMOOTH MUSCLE GROWTH

The generation of contractile force is one of the principal roles for bSMCs. Beyond the immediate effect of recruitment and longer contraction times, bladder response to increased work demand (i.e., increased outlet resistance) results in an increase in bSMC mass through hypertrophy (increase in cell number) and hyperplasia (increase in cell size). bSMC growth has been shown to increase in response to growth factors, such as basic fibroblast growth factor (FGF2),[104–106] platelet-derived growth factor BB (PDGFB),[74] and heparin-binding EGF-like growth factor (HBEGF),[107] though other mitogenic signals (e.g., mild hypoxia) may be important. In many instances, the transcription of specific genes eventually leads to increased cell mass and/or number and is mediated through MAPKs,[108] STAT3, AKT, and mTOR, although other kinase signaling families are probably involved (Figure 48.1). These bioactive peptides contribute to tissue expansion through autocrine and paracrine signaling mechanisms. It has become increasingly clear that diverse signals can participate in a number of positive and negative feedback loops, which may amplify or reduce the initial stimulus, differentially contributing to specific DNA transcription, protein synthesis, and inactivation of proapoptotic pathways. There exists considerable interest in the modulation of the bSMC mitogenic response, as it is believed that progressive increase in smooth muscle mass is a key component of bladder dysfunction. Currently, management of bladder wall thickening is based on the use of anticholinergics, such as oxybutynin and tolterodine. Interestingly, besides its well-described antimuscarinic effect, oxybutynin inhibits serum-induced bSMC proliferation and gene expression in vitro, giving us another potential explanation for its proven clinical efficacy.[109] Other molecules, such as botulinum toxin, which target the muscarinic pathways, have appeared in experimental clinical use based on an acceptable clinical response in other conditions.[110–113] Known to have a chemodenervating effect based on skeletal muscle studies, the different toxin serotypes (BTX A–G) target different proteins involved in the SNARE (soluble N-ethylmaleimide-sensitive factor attachment protein receptor) complex (Figure 48.2).[110] The mechanism of action in smooth muscle, however, may be more complex, as new evidence suggests an antinociceptive and neuromodulating effect.[112,114,115] Recent clinical trials in pediatric and adult populations have demonstrated variability in the degree of efficacy for inhibition of spasticity and improvement of quality of life.[116–122]

Once the pathways of the mitogenic response are better elucidated, specific inhibitors may lead to clinical trials. In one example, a recent area of interest has been the regulation of compensatory bladder hypertrophy with calcineurin inhibitors, such as cyclosporine and FK506 (tacrolimus). Initial evidence suggesting modulation of muscle hypertrophy has been described in a bladder outlet obstruction animal model.[77] mTOR signaling was also shown initially to be beneficial for preventing muscle growth and remodeling in vitro,[82] and recently to prevent remodeling, overgrowth, and hypertrophy of bladder muscle in vivo.[124] This type of in vitro to in vivo

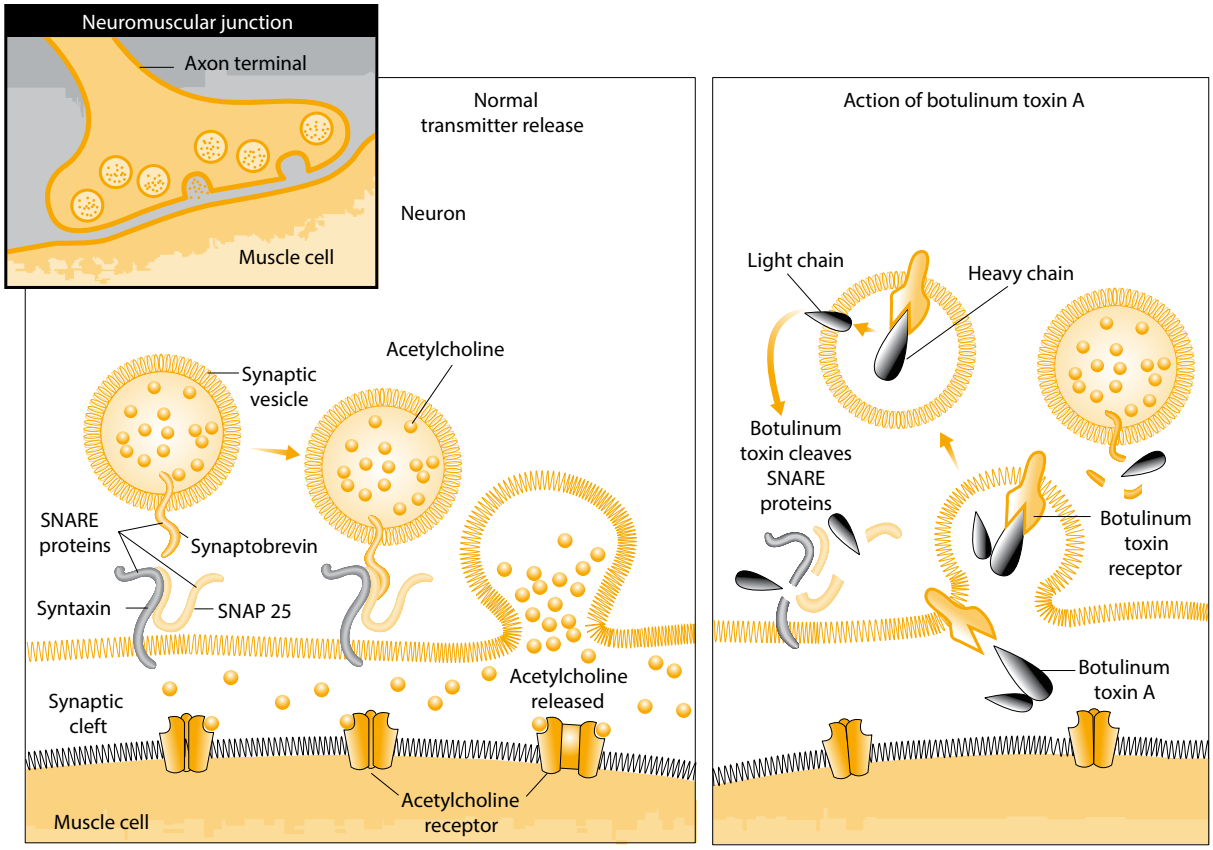

FIGURE 48.2 Under normal conditions, acetylcholine is packaged in vesicles that fuse with those of the nerve terminals, releasing the transmitter into the synaptic cleft. This process is mediated by a series of proteins, collectively called the SNARE proteins. Botulinum toxin cleaves the SNARE proteins, preventing assembly of the fusion complex and thus blocking the release of acetylcholine. (Adapted from Rowland LP. *N Engl J Med* 2002;347:382–3. With permission.)

work may lead to translational venues for new pharmacologic therapies.

Several elegant studies have suggested that different stretch-induced growth factors contribute to bladder impedance pathology, by increasing hypertrophy, although these proteins are by no means the exclusive mediators of bSMC mechanical responses. For instance, studies of the COX pathway have suggested that COX-2 expression—active during bladder development[125]—is reexpressed during bladder distention[64] (making COX-2 inhibitors potential pharmacologic inhibitors of stretch-induced bSMC proliferation). These observations suggest that obstruction response may reactivate certain fetal gene expression patterns. Teleologically, this may represent an effect to restore the function originally intended during development, such as concurrent growth and differentiation. Convergence of these protein and enzymatic pathways in the regulation of bladder obstruction has yet to be demonstrated.

EXTRACELLULAR MATRIX REMODELING

As the bladder develops, or adapts to different stimuli, the ECM also remodels in concert with the changes described for bSMCs (for a review, see Aitken and Bagli[85,86]). An important group of enzymes—the matrix metalloproteinases (MMPs)—are crucial in this process of altering the ECM structure and function. They are multifunctional proteases that degrade ECM proteins, liberate or modulate the bioactivity of growth factors and cytokines of other proteases, and alter the biophysical characteristics of the matrix. A cascade of events is initiated in the setting of excessive distention or high-pressure emptying, slowly resulting in thickening of the bladder wall. In conjunction with bSMC hyperplasia and hypertrophy, there is an increase in collagen synthesis, with deposition of collagen I and III,[126] associated with increased expression of MMP-2 and MMP-9, which are MMPs known to have an active role in matrix turnover in animal models.[127] While collagen expression may increase, the enzymes responsible for remodeling are also altered. With increased MMP-7 expression and activity in the bladder, the collagen type I and III fibrils appear to be decreased in integrity, leading initially to an increased intraluminal volume in the bladder.[124]

While the bladder matrix contributes to the physicomechanical characteristics of bladder dysfunction, it is proving to directly orchestrate bSMC biologic responses as well. The prototypical matrix protein in the bladder is fibrillar collagen. Stretching bSMCs promotes collagen production, and bladder obstruction models have demonstrated

the new expression of both protein and collagen mRNA within the muscle bundles. Mostly, types I and III are associated with the detrusor, although 19 different collagen types have been identified so far in other tissues, some with structural roles and others that associate with the structural types. For example, type XII collagen contributes to cross-linking type I fibrils during fiber assembly and may contribute to stiffness of tissues. Furthermore, type XII mRNA expression increases during mechanical distention of the whole bladder.[128] Diverse matrix alterations (accumulation, breakdown, redistribution, and structural rearrangements) are all occurring when tissues are remodeled during development, as well as during response to injury or wound repair. In fact, many biologic mechanisms in development are recapitulated during repair. MMPs are enzymes with the ability to edit matrix collagen, as well as many of the other ECM proteins. Although MMPs are now known to perform a variety of functions, they are best known for their originally described ability to break down (proteolyse) the ECM during morphogenesis, cell (tumor) invasion, and wound repair. Increased MMP activity or production has been described during bladder development and bladder obstruction in animal models. However, it now appears that the alterations in collagen may directly stimulate bSMC growth. When collagen is denatured experimentally, it elicits a strong proliferative response in bSMCs. Similarly, when collagen is chemically proteolysed by MMPs, bSMC growth is stimulated.[72] The proteolytic fragments released from the degradation of fibrillar collagen generate different signals than intact collagen, and potentially modulate bladder remodeling and bSMC growth by differential signaling pathways.[82,129]

It is likely that the receptors on the surface of all cells, including bSMCs, which permit cell–matrix attachment, are recognizing new epitopes in ECM macromolecules exposed as a result of protease activity. Inhibition of matrix receptors, such as the integrins, can potentially prevent bSMC proliferation in response to proteolysed matrix. Since bSMCs themselves are producing the enzymes (MMPs) responsible for matrix rearrangement, a powerful dynamic reciprocity is being revealed wherein bSMCs cause matrix alterations, which can then directly stimulate bSMC growth. Since natural regulators or inhibitors of these molecules also exist in the bladder (tissue inhibitors of MMPs [TIMPs]), we begin to appreciate a complex set of balanced mechanisms that depend on cell–matrix interactions. These processes are probably disturbed during bladder obstruction responses.

Finally, an integral yet poorly understood and sometimes overlooked part of the ECM is composed of proteoglycans and glycosaminoglycans. For instance, they may serve as ligands for some of the collagens present in the bladder wall and mediate response to injury or hyperdistention.[128] Most of the current research regarding these molecules has been directed toward the urothelium, use in reflux, and the protection of this layer against noxious stimuli, which is probably disrupted in conditions such as interstitial cystitis.[130] The accumulation of ECM proteoglycans and glysosaminoglycans is a known integral part of the early phases of tissue response to injury, conditioning changes in the ECM that may serve to direct the later deposition of the structural collagens. Evidence for a role in bladder wall remodeling comes from studies on the receptors for the ubiquitous glycosaminoglycan, hyaluronic acid, a molecule that appears to play a role in bSMC collagen gene expression and regulation during distention.[128,131]

NEUROTRANSMITTERS AND NEUROTROPHIC FACTORS

Bladder function is tightly regulated mainly under the influence of nervous and hormonal control systems. To date, the muscarinic receptors seem to be the most important class of receptors involved in the activation of detrusor contractions.[48,132] The human bladder expresses all known cholinergic muscarinic receptors (CHRM1–5),[133] with a predominance of CHRM2 and 3 subtypes,[134] depending on the species studied. The CHRM3 receptor is the primary receptor linked to stimulation of detrusor contraction through activation of phosphoinositide hydrolysis and generation of inositol triphosphate, although CHRM2 quantity predominates in the human bladder by a ratio of at least 3:1 over CHRM3. Interestingly, human bSMCs demonstrate a requirement for lipid raft and cholesterol during muscarinic signaling not seen in other species. Notwithstanding the unclear functional role of the M2 receptor, it is interesting to note that its expression and activity further increase in experimental pathologic states and by M3 selective antagonist treatment, potentially facilitating bladder contractions and muscle hypertrophy.[135–138] Interest in the M2/M3 receptor differences has been rekindled after the recent introduction of subtype-selective pharmacologic agents, i.e., M3-specific antagonists solifenacin and darifenacin.[139]

Other pathways are clearly important in modulating the M2/M3 response or even instigating contractile responses on their own in normal and pathologic circumstances. Prostacyclins have long been known to initiate contractile responses. Also, adenyl cyclase purinergic and androgen signaling can alter muscarinic activation. Endothelin acting on the ETA/B receptors is able to initiate contraction in bSMCs in nonmuscarinic pathways. Other neurotrophic factors and cooperative receptors—such as the NGF, BDNF, Ca^{+2}, and K^{+} channels and adrenergic receptors—have been gaining relevance.[48,140–143] While neurons in the interstitial spaces transmit signals to the bSMCs, the urothelium can engage in the contractile process, through transient receptor potential vanilloid 4 channel (TEPV) and purinergic signaling. However, an understanding of the pre- and postnatal development of these other pathways is needed to clear the way for new approaches to disease. Regarding congenital disorders, the issue is compounded by the limited understanding of neural control and maturation during development. Fetal human studies have shown variation in some receptor subtype expression when compared with adults, as is the case for P2X receptors.[144] In contrast, fetal versus adult reports describe little difference in cholinergic innervation in response to stimulation by muscarinic receptors, suggesting functional capacity early in life.[145] PUVs and experimental bladder obstruction, however, result in altered capacity for contractility in response to acetylcholine.

POSTERIOR URETHRAL VALVES AND CONGENITAL BLADDER OUTFLOW OBSTRUCTION

How the underlying molecular signaling cascades mediate survival, contractility, growth, and cell death can help lay the foundations for understanding how extrinsic pathologies mediate intrinsic bladder responses. PUVs represent an archetypical form of increased resistance to urinary flow in humans. In the pediatric sphere, this is somewhat analogous to the impedance generated by benign prostatic enlargement in the adult male. Whereas similar clinical bladder responses are noted between these two pathologies, multiple factors probably differentiate childhood from adult obstructive uropathies. PUV bladder trabeculation and altered function represent a spectrum of pathology that may derive as much from its timing during gestation as from the degree of impedance. Experimental observations on extrinsic manipulation of the bladder neck would suggest that while extrinsic obstruction models do reproduce some of the structural and functional consequences seen in clinical PUV bladders, they may also unwittingly distract from the true nature of the problem at the molecular level.

The "valve" bladder has long been viewed as the bladder's response to a mechanical problem. bSMCs must simply work harder to expel urine. They must mount an increased contraction effort. In doing so, the bladder phenotype (structure and function) changes. Finely tuned neurosensory perception of pressure and stretch, which accompanies higher than expected voiding pressure, is related through reflex arcs and may increase efferent motor demands on the detrusor. Furthermore, abnormalities in the outlet region of the bladder neck and sphincter areas, which harbor the valves themselves, may give rise to neurodevelopmental changes that directly influence bSMC function. Nevertheless, the apparent normalization of PUV bladder morphology and function can occur when valves are ablated, suggesting that bSMCs retain the capacity for normal function despite the creation of an outlet defect during gestation. In contrast, bSMCs from neurogenic bladders appear to harbor more permanent phenotypic changes, which are retained during in vitro culture compared with normal bSMCs.[146,147] It is not known if obstructed bSMCs retain hypertrophic phenotypic changes as well, although obstructed bSMCs in experimental models do not completely return to normal function and morphology after release of the obstruction.

During development and the periods of normal unobstructed emptying, bSMCs are programmed to accept and work against a range of elevated intravesical pressures. The resistance afforded by PUV increases this pressure. Whether indirectly through a stretch- or tension-neural receptor mechanism and/or directly via smooth muscle cell stretch or mechanoreceptors, alterations in muscle membrane ion channels, muscarinic activity, or changes in smooth muscle cell shape, bSMCs contract more forcefully. As inefficient emptying progresses, the excessive bladder storage may actually overstretch the detrusor muscle to excess degree and duration; indeed, this may become a dominant insult that erodes bladder function.

Clearly, the role of physical stretch and tension in bSMC biology is more complex and difficult to sort out from a mechanistic point of view than it first appears. We now appreciate that stretch operates under different conditions in different pathologies, and may contribute to bladder alterations at different points in natural history of any given obstructive uropathy. The paradox is that although mechanical stretching of bSMCs in vitro may generate clinically familiar responses generated by hypercontraction or excessively stretched bSMCs in vivo, it may do so through physiologically irrelevant or unrelated molecular mechanisms. To determine whether the physical stimulus of stretch per se can predict and elucidate relevant changes in bSMC phenotype, mechanical stretch of bSMCs in vitro should be followed by studies in vivo. Studies of this nature have provided compelling information and suggest that bSMCs alone may be a primary cellular recipient of relevant stretch (mechanical) stimuli in vivo.

LIMITATIONS OF RESEARCH TOOLS: IN VIVO, EX VIVO, AND IN VITRO MODELS

The study of any biologic problem is often dependent on the availability of appropriate models. More importantly, suitably framed segments or aspects of each problem should guide investigation. As previously mentioned, these emerging segments include proteins and molecules, which affect smooth muscle cell growth and phenotype, the influence of mechanical and neural stimuli, and the role and regulation of the bladder ECM components. Clearly, these areas of investigation will intersect and new segments of the problem are to be anticipated. Although none of the molecules currently reported to influence bSMC growth and behavior in the context of bladder obstruction have affected clinical practice yet, they may hold keys to appreciating how bSMCs work and respond to pathogenic stimuli. There are, however, conceptual shortcomings to the use of in vitro, ex vivo, and in vivo animal models as a means of deciphering the intricacies behind normal and pathologic bladder function and development. Experimental conditions differ in timing, reversibility, stretching parameters, and cyclicity,[71,72,82,148,149] as well as the nature (extrinsic vs. intrinsic) of the obstructive stimuli. In some instances, the in vitro and ex vivo models are recapitulated in vivo, while in others, the in vivo models do not respond as positively to treatments. Assessments of potential pharmacotherapies in experimental in vivo models most often begin soon after obstruction during the initial inflammation, hypoxia, and stretch injury, rather than close to or soon after the time of surgical reversal of obstructions, as would occur clinically. Therefore, the results observed are potentially not directly translatable to treatment of the detrusor in congenital anomalies.

THE PROMISE OF TISSUE ENGINEERING AND STEM CELLS

As the full potentials of molecular mechanisms and therapeutics, prenatal diagnosis, and sheer curiosity about

bladder disease are awakened and converge in the coming decade, we can expect new and frankly unexpected approaches to emerge for the treatment and even prevention of obstructive bladder pathologies. Increasingly, intense research has focused on the fields of regenerative medicine and tissue engineering, as the principles of bioengineering, biomaterials, and cell transplantation are applied to construct biologic substitutes that would restore function in diseased urologic tissues.[150] This process has uncovered that, perhaps not unexpectedly, the biology of the bladder is every bit as complex and enigmatic as that of the other vital body systems.[151] It has proven difficult to regenerate all the functional layers of the bladder, as the engineered tissue needs to have optimal mechanical and structural characteristics while being biocompatible and capable of eliciting enough neovascularization to survive once implanted. Much of the available data are based on in vitro and promising animal models[86,152] that take into consideration the developmental and environmental stimuli that are necessary for the appropriate growth and differentiation of bSMCs[153–156] and fully functional urothelial sheets.[102,157]

Another avenue has explored the potential for various sources and types of stem cells to regenerate or de novo tissue engineer functional tissue. Regarding de novo tissue engineering efforts with stem cells, many of them have faced the same issues as using endogenous bSMCs and urothelial cells. Stem cells do not always differentiate as expected, although the potential of recapitulating development through the use of pluripotent or multipotent stem cells remains a desirable but difficult goal.[158,159] In contrast, exogenously derived stem cells may provide a supportive role in the tissue, encouraging the endogenous cells to repair the tissue.[160] Regeneration can also occur through endogenous precursor and progenitor cell populations, including those in the lamina propria, the interstitial detrusor regions, and the urothelium itself.[161–166]

A further issue is that autologous cells from patients with nonmalignant disease do not perform as well as normal controls, including urothelial cells.[167,168] A greater understanding of these lasting changes in cell physiology of autologous donor cells, which may be due to an underlying defect in the cells predisposing the organ to dysfunction, self-sustaining transcriptional networks, or even epigenetic change, will be crucial for tissue engineering and regeneration efforts.

CONCLUSION

The past decades have witnessed a changing view of the bladder, from a simple organ that contracts in order to volitionally eliminate urine, to a complex unit responsive to fine neuromodulation and smooth muscle–ECM interaction. As such, the approach to bladder dysfunction is shifting from a symptomatic basis (based solely on treating urinary tract symptoms, incontinence, high intravesical pressures, and capacity) to measures aimed at preventing end-stage damage to affected organs (which requires aggressive and morbid interventions, such as augmentation cystoplasty or renal transplantation). In the latter approach, the tendency is to prevent the overgrowth of smooth muscle, inflammatory and fibroproliferative responses, and its consequent loss of compliance, contraction inefficiency, and hyperdistention. Even though great advances have been made in the past few decades, understanding molecular mechanisms behind bladder development and the bladder's transcriptional and epigenetic responses to abnormal mechanical states remains a fertile area for research and development. As such, our molecular understanding of the pathophysiology of the bladder is moving us closer to translatable goals of newly targeted therapies for bladder conditions.

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CHAPTER
49

Embryology of the Anterior Abdominal Wall, Bladder, and Proximal Urethra

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ANTERIOR ABDOMINAL WALL

During the first 3 weeks of development, the embryo is a plate of cells, the embryonic disk, whose ventral surface is a membrane called the somatopleure. The anterior abdominal wall is at first represented by the somatopleure of the overhanging head and tail folds. The somatopleure closes concentrically from the cranial, caudal, and lateral margins, centering on the future umbilical ring (Figure 49.1).

In the sixth week of development, the midgut closes and the body stalk reduces in relative size. The somatopleure is invaded by mesoderm from myotomes on either side of the vertebral column. This mesoderm migrates laterally and ventrally as a sheet (Figure 49.2).

The primordia of the two rectus abdominis muscles form laterally and begin to move toward the midline during the seventh week. At that time, the mesoderm laterally splits into three sheets, eventually producing the external oblique muscle, the internal oblique muscle, and the transversus abdominis muscle. These layers are all recognizable during the seventh week (Figure 49.3). In the infraumbilical area, the formation of three muscle layers is preceded by invasion of secondary mesoderm that arises from the primitive streak just behind the cloaca. This secondary mesoderm then surrounds the cloaca and invades the body wall caudal to the body stalk, providing primary closure to the body wall between the phallus and the body stalk and forming part of the anterior bladder musculature as well (Figure 49.4).[1] Between the 7th and 12th weeks of development, the rectus abdominis muscles meet in the midline except around the umbilicus. During this same time, the secondary mesoderm forming the lower abdominal wall is reinforced externally by invading somatic mesoderm that forms the muscular layers of the lower abdominal wall.

The exact genetic and cellular elements necessary for abdominal wall development are for the moment unclear. Mycotoxins, given to mice in early development, result in extensive abdominal wall defects, suggesting that failure of cell proliferation, cell migration, and/or production of extracellular matrix materials within the mesoderm itself can lead to abdominal wall defects. Other elements necessary for normal fusion and closure are (1) synthesis of a glycoprotein surface coat on each opposing fold to promote adherence, (2) apoptosis of some cells while others migrate in, and (3) cell-to-cell contact to permanently bond two sides together.[2] *The important urologic anomalies resulting from faulty embryogenesis of the abdominal wall are the Eagle–Barrett (prune belly) syndrome and exstrophy of the bladder or cloaca. Neither of these is an arrested stage of normal embryogenesis.* The Eagle–Barrett syndrome seems most likely to be due to faulty mesodermal development during the 6th to 12th week, as several mesodermal elements (abdominal wall, ureter, bladder, and testes) are usually involved.[3] Recent reports of prune belly syndrome with chromosome 17q12 deletions involving the HNF1 gene (a gene that regulates mesodermal and endodermal development) would support this theory and suggest a genetic basis for the problem.[4,5] Another theory states that the Eagle–Barrett syndrome is a deformation of the abdominal wall produced by distended viscera or increased intra-abdominal pressure.[6] Support for this theory is found in the observation that fetal ascites can result in congenital hypoplasia of the abdominal wall.[7] In addition, there is a report of a mutation of muscarinic acetylcholione receptor M3 producing a problem with bladder contraction and a prune belly–like syndrome in five brothers.[8] A third theory attributes the urinary abnormalities to a primary abdominal wall defect resulting in decreased intra-abdominal pressure.[9]

Exstrophy may result from a failure of the secondary mesoderm to cover the infraumbilical abdominal wall. Rupture of the cloacal membrane prematurely could also produce such a failure. Should this occur in the fifth week, cloacal exstrophy could result.[10] If this does not occur until the seventh week, so that some of the secondary mesoderm is in place, classical bladder exstrophy might result. Still later (the 10th or 11th week), failure of invasion by somatic mesoderm might result in superior vesical fissure or epispadias. There have been sporadic reports of familial instances of the exstrophy–epispadias complex. There also have been studies that suggest that there may be a site on chromosomes 4 and 19 that contains a gene for an autosomal recessive form of the exstrophy–epispadias complex.[11]

Lower Urinary Tract

The development of the lower urinary tract is closely interrelated with that of the genital tract and the hindgut, but for clarity, the genital tract is discussed later.

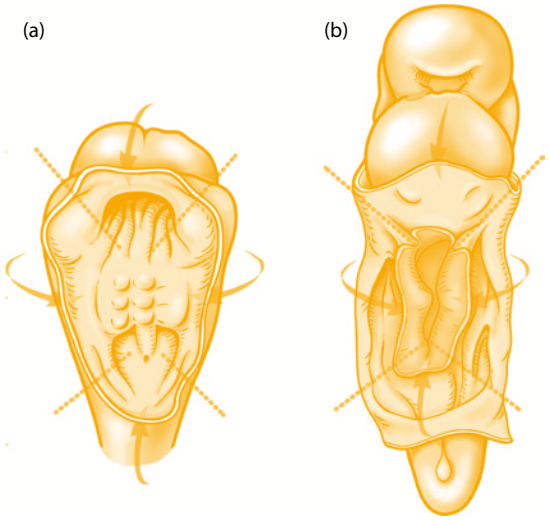

FIGURE 49.1 Ventral views of human embryos of 2 and 3 mm. The body stalk has been cut distal to the site of the future umbilical ring. Arrows show the direction of infolding; dotted lines indicate the arbitrary boundaries of the four infoldings. (Reproduced from Gray SW, Skandalakis JE. *Embryology for Surgeons*. Philadelphia: WB Saunders, 1972, 496. With permission.)

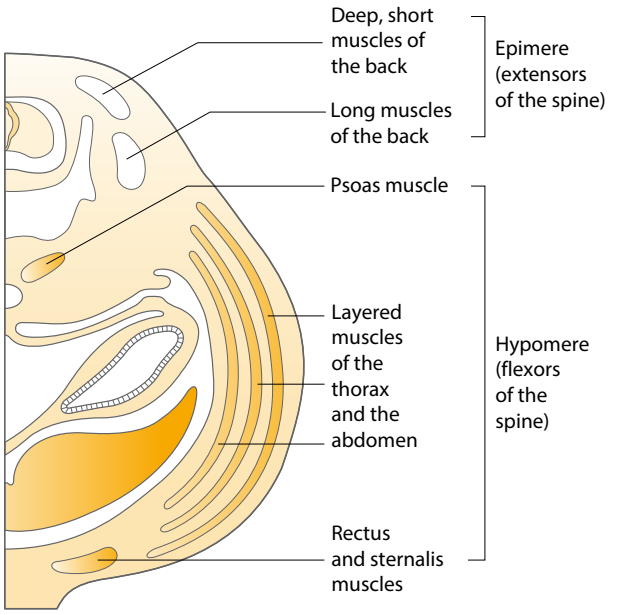

FIGURE 49.3 Diagrammatic transverse hemisection through the abdomen or thorax of a 7-week human embryo. (Reproduced from Arey LB. *Developmental Anatomy*, 6th edn. Philadelphia: WB Saunders, 1974. With permission.)

During the first 3 weeks, the cloaca develops from endoderm as a blind caudal expansion of the hindgut (Figure 49.5). The hindgut meets the ectoderm of the body wall at the cloacal membrane. This membrane extends caudally from the primitive streak and is turned under by the tail fold. It extends from the tail bud to the body stalk. As the mesoderm grows, the area of the cloacal membrane is decreased. The cloaca gives off a ventrally directed allantoic stalk and receives the mesonephric duct laterally and extends caudally as the tail gut.

The cloaca, during the fifth week, is divided by opposing walls of the hindgut in the allantois, meeting in a saddle-shaped notch with its apex pointing caudally. This notch fills in with mesenchyme to form the urorectal septum. This septum pushes caudally as a fold and advances, dividing the cloaca into the primitive rectum posteriorly and a urogenital sinus anteriorly (Figure 49.6).

Various regions of the urogenital sinus are recognizable in the sixth week: the allantois, bladder, pelvic, and phallic portions of the urogenital sinus. The pelvic portion of the urogenital sinus lies cephalad to the entrance of the mesonephric duct but below the bladder, whereas the phallic portion of the urogenital sinus lies caudad to the entrance of the mesonephric duct and extends distally toward the genital tubercle.

By the seventh week, the ureters empty into the bladder by a process in which nephric ducts, after the ureteral buds have appeared, are absorbed into the urogenital sinus and acquire four separate openings into the sinus (Figure 49.7). The mesonephric ducts are shifted further caudad in the sinus and come to lie close to each other at Müller's tubercle, while the ureters shift cephalad and laterally into the bladder. It is then that the trigone is formed. The trigone is temporarily mesodermal but fills in with urogenital sinus

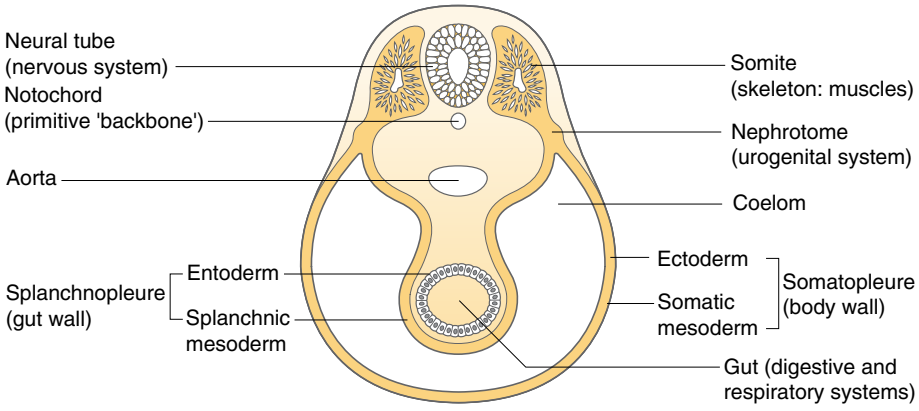

FIGURE 49.2 Diagrammatic transverse section of a vertebrate embryo. (Reproduced from Arey LB. *Developmental Anatomy*, 6th edn. Philadelphia: WB Saunders, 1974. With permission.)

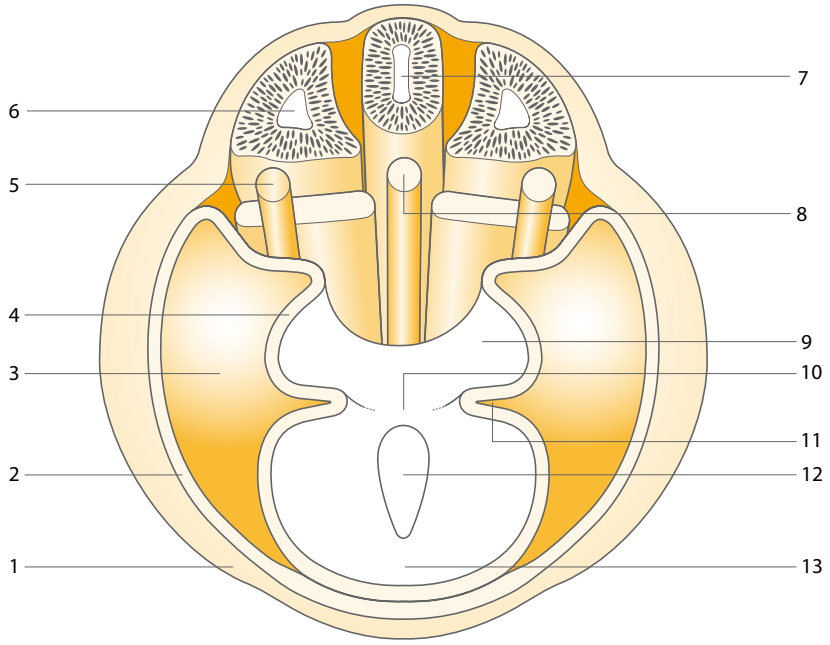

FIGURE 49.4 Disposition of mesoderm at the caudal end of a somite embryo as viewed working down from inside the caudal end of the embryo: (1) surface epithelium; (2) somatic layer of the lateral plate mesoderm; (3) coelomic cavity; (4) visceral layer of the lateral plate mesoderm; (5) nephrogenic cord; (6) somite; (7) neural tube; (8) notochord; (9) unsegmented paraxial mesoderm; (10) primitive streak; (11) site of developing urorectal septum; (12) site of cloacal membrane; (13) infraumbilical abdominal wall. (Reproduced from Glenister TW. *Br J Urol* 1958;30:117. With permission.)

epithelium, so that it, too, is eventually endodermal. The bladder epithelium at this time consists of a single layer.

The urorectal septum reaches the cloacal membrane and divides the cloaca into the urogenital sinus and the rectum; the cloacal membrane then ruptures (Figure 49.6). The caudal edge of the urorectal septum, which is covered with endoderm, is exposed as the perineal body. It merges with lateral folds flanking this fissure and becomes covered with ectoderm. It is eventually marked by a median raphe and becomes the perineum. Hillocks behind the anus encircle this area and form the anal canal, which eventually becomes lined with ectoderm.

In the eighth week, the bladder muscle begins to appear as a longitudinal layer on the dorsal surface of the bladder. By the ninth week, the bladder cavity begins to expand into a sac, the apex of which (the urachus) is elongated.

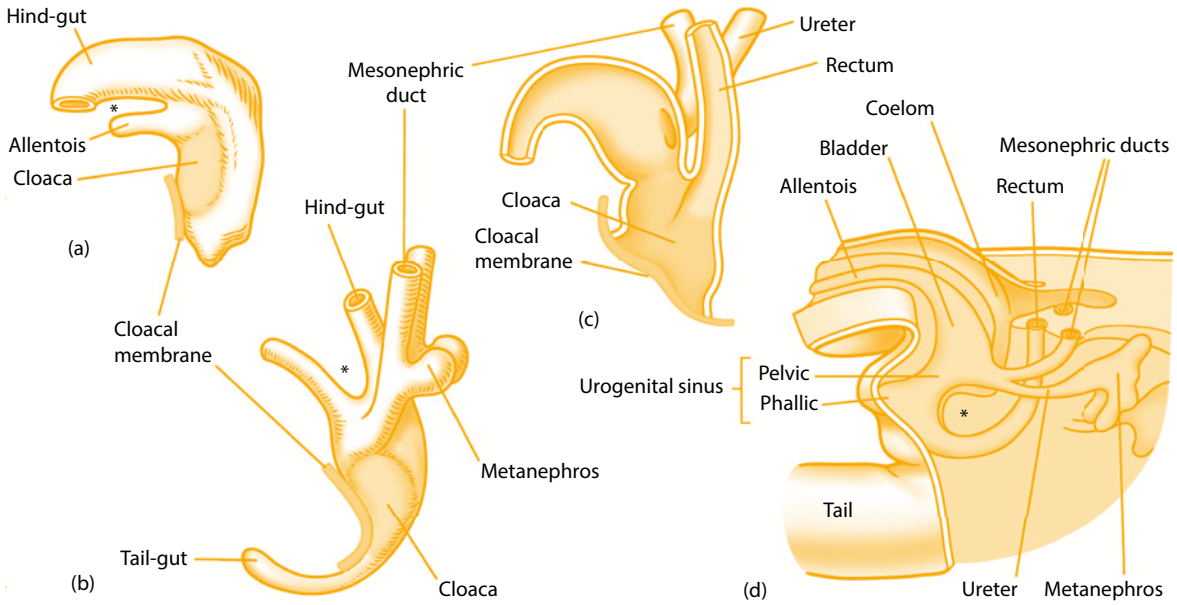

FIGURE 49.5 Division of the human cloaca: (a) 3.5 mm stage; (b) 4 mm stage; (c) 8 mm stage; (d) 1 mm stage. The asterisks in (a), (b) and (d) indicate the cloacal septum. (Reproduced from Arey LB. *Developmental Anatomy*, 6th edn. Philadelphia: WB Saunders, 1974. With permission.)

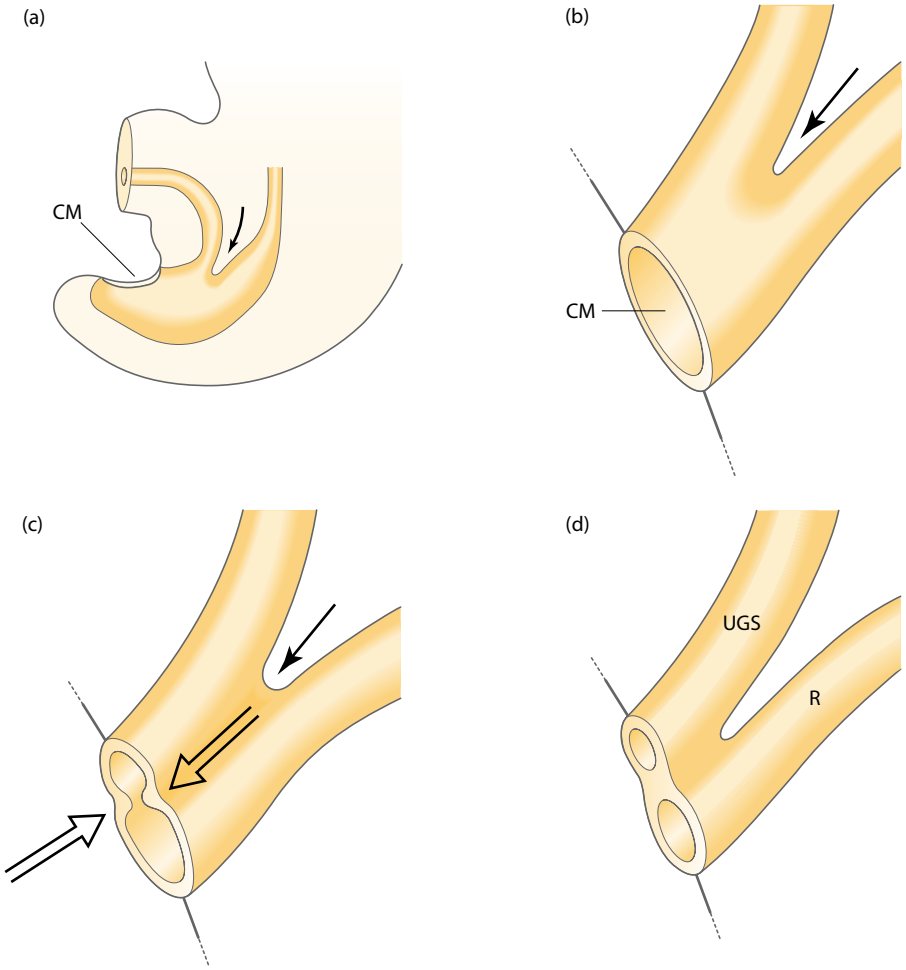

FIGURE 49.6 Septation of the cloaca. (a) Lateral view of caudal embryo (CM, cloacal membrane). Septation of the cloaca occurs in a coronal plane as Tourneux's fold (b) extends to the cloacal membrane from above, and (c) as Rathke's plicae extend towards each other from the sides. (d) Septation establishes the primitive urogenital sinus (UGS) and rectum (R). (Reproduced from Stephens FD, Smith ED. *Anorectal Malformations in Children*. Chicago: Year Book, 1971. With permission.)

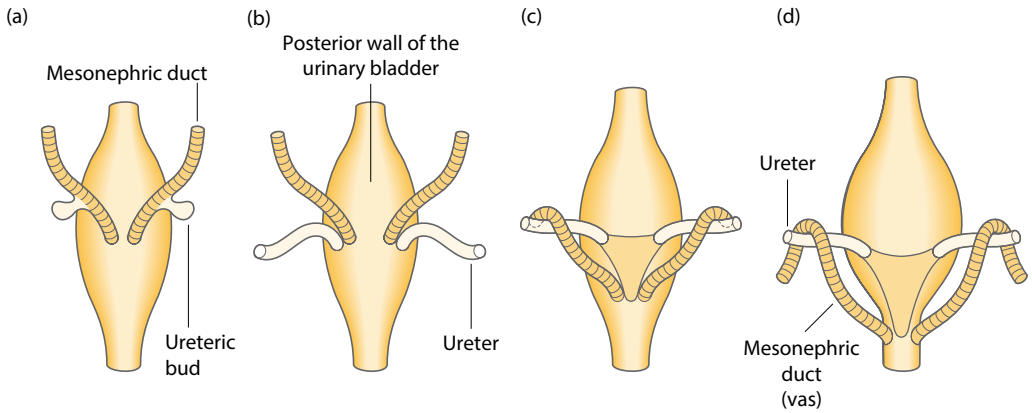

FIGURE 49.7 (a–d) Dorsal views of the bladder to show the relationship of the ureters and mesonephric ducts during development. Initially, the ureters are formed by an outgrowth of the mesonephric duct, but with time they assume a separate entrance into the urinary bladder. Note the trigone of the bladder formed by incorporation of the mesonephric ducts. (Reproduced from Sadler TW. *Longman's Medical Embryology*, 7th edn. Philadelphia: Williams & Wilkins, 1996. With permission.)

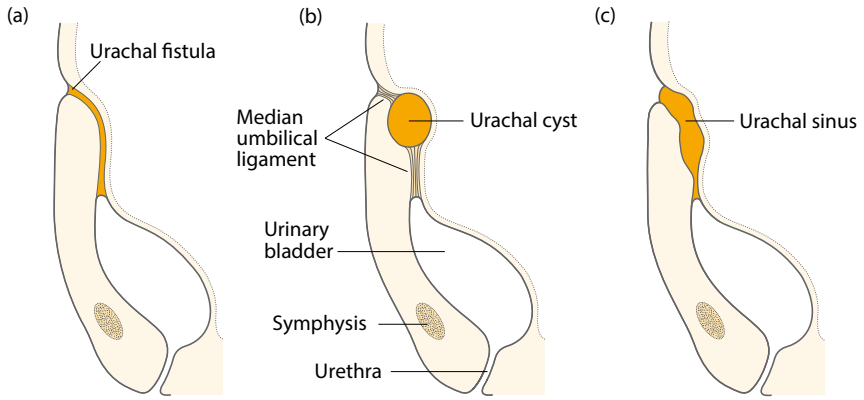

FIGURE 49.8 Diagrams of (a) urachal fistula, (b) urachal cyst, and (c) urachal sinus. The sinus may or may not be in open communication with the urinary bladder. (Reproduced from Sadler TW. *Longman's Medical Embryology*, 7th edn. Philadelphia: Williams & Wilkins, 1996. With permission.)

The urachus is continuous with the allantoic stalk at the umbilicus. The bladder and urachus elongate as the infraumbilical body wall forms from the somatic mesoderm.

In the 12th week, the bladder epithelium becomes transitional, and its muscular wall is formed from mesenchyme. The smooth muscle of the urinary tract is acquired in an ascending fashion from bladder to intrarenal collecting system.[12] The bladder epithelium over the ureteral orifice forms Chwalla's membrane, which temporarily covers and occludes the ureteral orifice. Chwalla's membrane perforates and the ureter becomes continuous with the bladder. By the 16th week, the bladder is completely muscularized and the urachus is closed.

Agenesis of the bladder is a rare anomaly that may arise because the allantoic stalk fails to develop.[13] However, if migration of the ureters and formation of the trigone are the events that induce enlargement of the allantoic stalk, then bilateral failure of ureteral migration with resultant ureteral ectopia would result in the same anomaly.

Urachal anomalies (patent urachus, urachal cyst, urachal sinus, and urachal diverticula) may be encountered clinically (Figure 49.8). Some result from a general mesodermal failure (the urachal diverticulum of the Eagle–Barrett syndrome);[3] however, most seem to result from delayed closure of the urachus. Lower urinary tract obstruction before 12 weeks of age (by virtue of bladder distension) could prevent closure.[14] There is, in addition, a definite association of patent urachus with upper tract problems, and therefore the entire urinary tract should be investigated.[15] Urachal cysts and sinuses presumably result from incomplete closure of the urachus.

Duplications of the bladder and urethra are usually associated with other hindgut and lower spinal cord duplications. Hence, it would appear that these result from a splitting of the hind end of the embryo at a very early stage of development, distinct from the lower abdominal wall defect resulting in exstrophy.

Ureteral ectopia, vesicoureteral reflux (VUR), and paraureteral diverticula appear to arise because the ureteral bud appears at a locus on the mesonephric duct more craniad or caudad than normal. As the ureter is incorporated into the urogenital sinus, its final site would be more craniad and lateral or caudad, respectively. The former results in VUR and diverticula, whereas the latter results in ureteral ectopia.[16]

Ectopic ureteroceles probably result from abnormalities of the ureteral bud, in addition to ectopia, and are often associated with renal dysplasia.[16] Intravesical (simple) ureteroceles are thought to be due to the persistence of Chwalla's membrane beyond the time when urine flow begins.[17]

Posterior urethral valves (type 1) may result from persistence of the path of migration of the mesonephric ducts distal to Müller's tubercle, so that they cross the urogenital sinus and enter anteriorly. Persistence of this portion coupled with anterior fusion might then produce the diaphragm known as valves.[18] Another type of valves (type 3) seems to result from persistence of the cloacal membrane at the junction of the end of the phallic portion of the urogenital sinus and the bulbomembranous urethra.[19]

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CHAPTER
50

Radiologic Assessment of Bladder Disorders

Douglas E. Coplen

INTRODUCTION

Congenital anomalies and abnormalities of the urinary bladder can be a significant cause of morbidity in infants and children. The function of the bladder may adversely affect the upper urinary tract and may impact urinary continence. Radiologic evaluation of the bladder and adjacent structures gives useful diagnostic information that directs therapeutic intervention. In children, ultrasonography is usually the initial diagnostic study. Fluoroscopic imaging (voiding cystourethrogram [VCUG]) is frequently obtained as indicated by the clinical history and ultrasound findings. Cross-sectional imaging (computerized tomography [CT] and magnetic resonance imaging [MRI]) is often used in complex cases where other imaging does not clearly define the anatomy.

Ultrasound is ideally suited for the evaluation of children with symptoms suggestive of a bladder or lower urinary tract abnormality because it is painless, is associated with no radiation exposure, and provides excellent anatomic definition of the bladder. For this study, a partially distended bladder is preferable. The clear differentiation between the anechoic urine and the bladder wall and surrounding structures enhances its diagnostic utility (Figure 50.1).

If upper urinary tract dilation is identified during an examination, the ultrasound should also include imaging after bladder emptying since the degree of bladder distension may affect the upper tract findings. Doppler ultrasound can be used to identify ureteral jets (urine flow into the bladder) (Figure 50.2) that are evidence of antegrade flow into the bladder.[1] Postvoid views can be obtained to assess bladder emptying and bladder wall thickening. Bladder volume can be estimated by ultrasound using the empirical equation Bladder volume = 0.7 × Width × Length × Depth.[2]

The VCUG is the best method of fluoroscopic bladder imaging. The study consists of direct opacification of the bladder with iodinated contrast medium that is usually instilled through a urethral catheter. Preferably both filling and voiding views are obtained during the study. Dynamic visualization of the bladder may give very useful information regarding bladder function and disordered elimination. Voiding views are especially important in the male since abnormalities of the bladder outlet and urethra greatly impact the bladder.

If IV contrast is utilized for upper tract imaging, the excreted contrast gives passively filled bladder images. While this avoids urethral catheterization, the contrast is dilute and opacification of the bladder and urethra is often poor and may result in a nondiagnostic study.

CT and MRI give improved spatial resolution when compared with more commonly utilized imaging modalities. Images are obtained in an axial mode, but can be reformatted in both the sagittal and coronal planes. With current software, both planar reconstructions and three-dimensional reconstructions give excellent resolution.[3]

Superior soft tissue resolution is an advantage of MRI over CT. On T1-weighted images, the bladder wall may be indistinguishable from the urine, but on T2-weighted studies, fluid-filled structures like the bladder are very well defined (Figure 50.3).[4] Because of prolonged acquisition times, sedation is required in younger children. MRI is very expensive when compared with ultrasound and fluoroscopy and should probably be reserved for complex cases where anatomy is not well defined using other modalities.

BLADDER ENLARGEMENT

An enlarged bladder may be identified on physical examination. While bladder distension may be a normal finding prior to voiding, it may be indicative of significant bladder or urethral pathology. Congenital anomalies, such as spinal dysraphism and prune belly syndrome, should be evident on exam and help with the differential diagnosis. A thickened bladder wall on ultrasound is suggestive of bladder outlet obstruction, although when the bladder is markedly distended, wall thickening may not be readily apparent (Figure 50.4).[5] Ureteral dilation in the presence of bladder distension and a thin bladder wall are suspicious for high-grade vesicoureteral reflux (Figure 50.1).

A VCUG gives both the anatomic detail and functional information that define the etiology of bladder distension. Views of the urethra are essential in the evaluation of these children. Bladder trabeculation and cellules are commonly identified in children with posterior urethral valves or neurogenic bladder. Children with prune belly syndrome or megacystis or microcolon usually have large smooth-walled bladders (Figure 50.5).

URACHAL ABNORMALITIES

The urachus, sometimes called the median umbilical ligament, is usually obliterated by the 12th week of gestation.

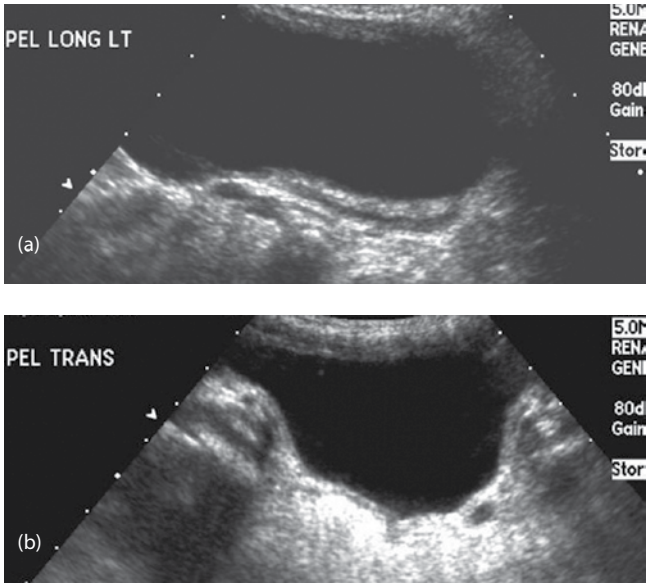


FIGURE 50.1 Bladder ultrasound obtained in a male with isolated bladder distension identified during pregnancy. Note the clear definition of the lumen and bladder wall on ultrasound. A dilated left ureter is seen posterior to the bladder. The child had bilateral grade V reflux but no infravesical obstruction.

In theory, a patent urachus may occur in the presence of bladder outlet obstruction, but no evidence of obstruction is identified in the majority of cases.[6] Occasionally, a patent urachus is identified at birth when there is free discharge of urine through the umbilicus (Figure 50.6). More commonly, only a tiny fistula is present and the umbilicus is enlarged or edematous. In these situations, the differential diagnosis includes omphalitis, "normal" hypertrophic granulation tissue, and a patent omphalomesenteric duct. Ultrasound may identify an inflamed tract (Figure 50.7). A fistulogram with radiopaque contrast is often diagnostic. Voiding cystourethrography is helpful in fully evaluating the lesion and any associated bladder outlet obstruction (Figure 50.6).

Partial obliteration of the urachus results in a urachal cyst. These are usually asymptomatic but occasionally become infected and are identified during the evaluation of lower abdominal pain, fever, and voiding symptoms.

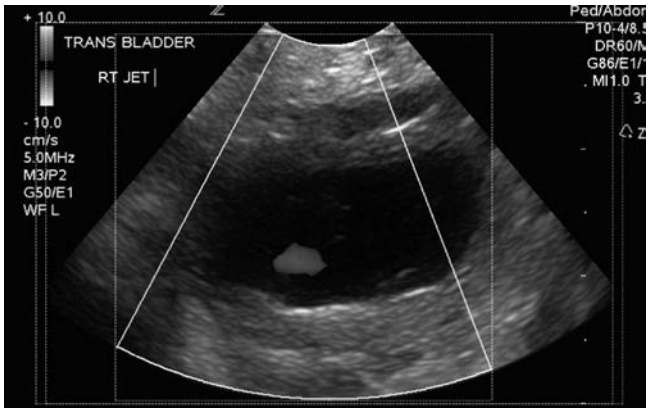


FIGURE 50.2 Bladder ultrasound utilizing Doppler to demonstrate urine flow from the right ureter into the bladder.

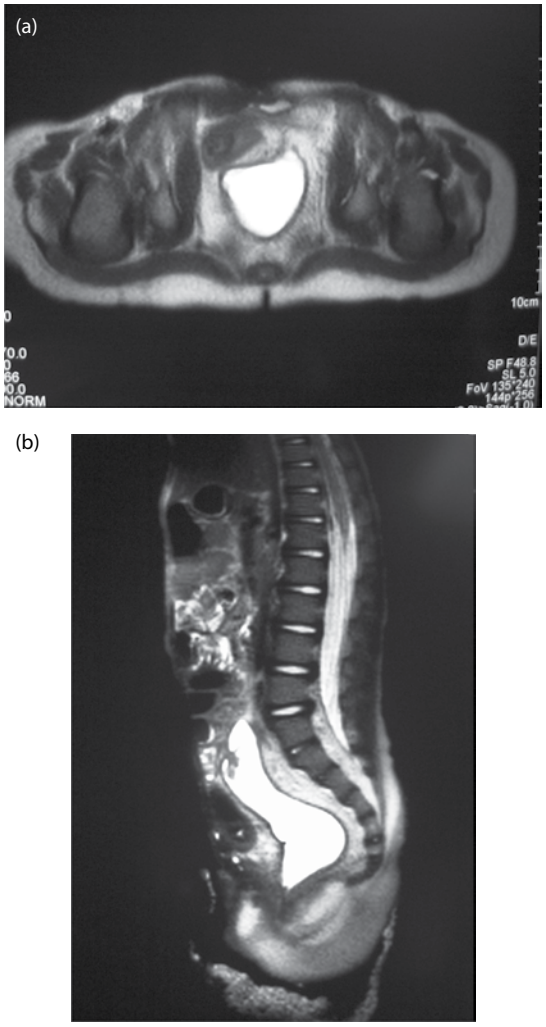


FIGURE 50.3 MRI obtained on a 6-year-old male with apparent history of bladder exstrophy based on physical examination. He is incontinent of both urine and stool per "rectum," but these do not appear to be mixed. The study clearly defines the lower tract anatomy. The ureters are reimplanted into a sigmoid segment (filling defect in bright structure (b)). The rectum is visualized anterior to the sigmoid "bladder" that has been pulled through posterior to the rectum (a).

FIGURE 50.4 Postvoid ultrasound in a boy with posterior urethral valves. There is a small postvoid residual, and marked bladder wall thickening is clearly apparent.

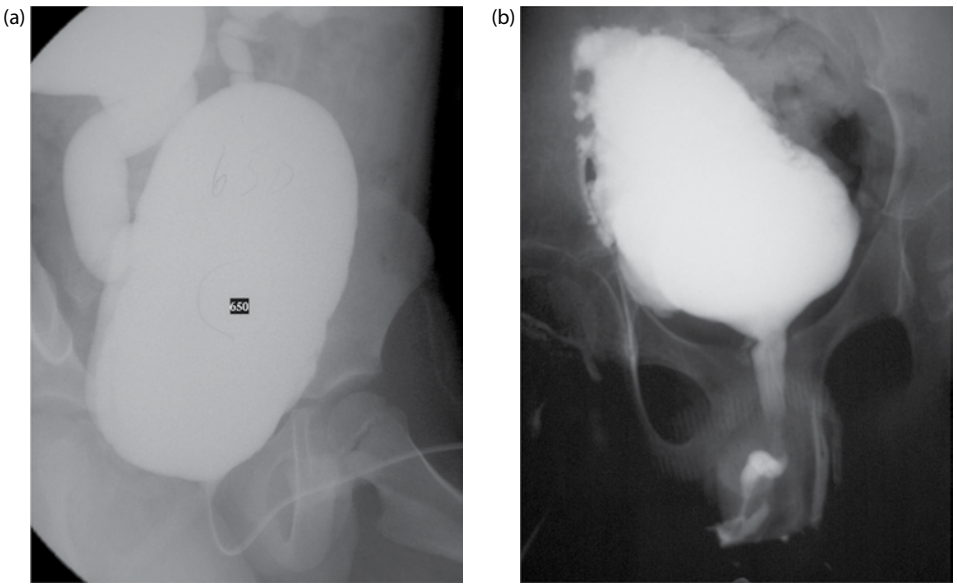


FIGURE 50.5 VCUG in two boys with bladder enlargement: (a) Bilateral high-grade reflux with a smooth bladder wall and no outlet obstruction. (b) Marked bladder trabeculation and "Christmas tree" deformity in a boy with spinal dysraphism.

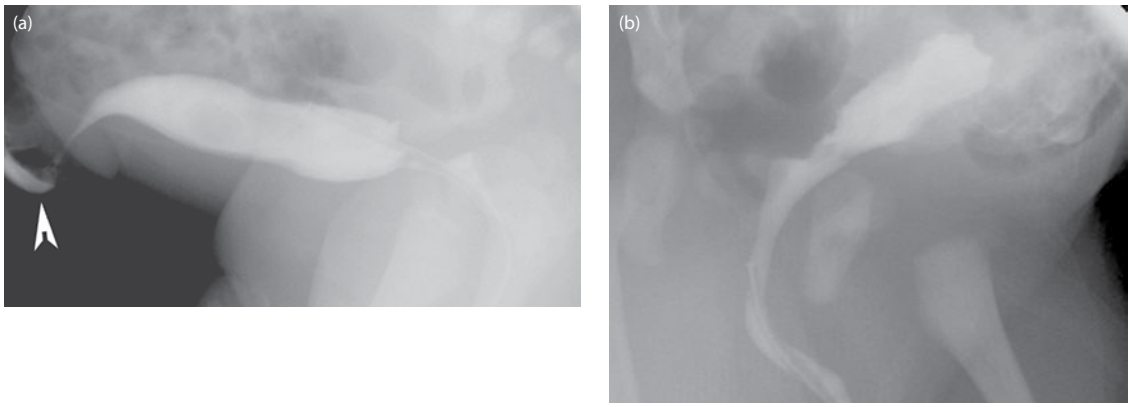


FIGURE 50.6 Newborn male with copious clear fluid drainage from the umbilicus. (a) Transurethral instillation of contrast shows free drainage out of a patent urachus onto the lower abdominal wall (arrow). (b) Voiding views show a normal urethra with no evidence of bladder outlet obstruction.

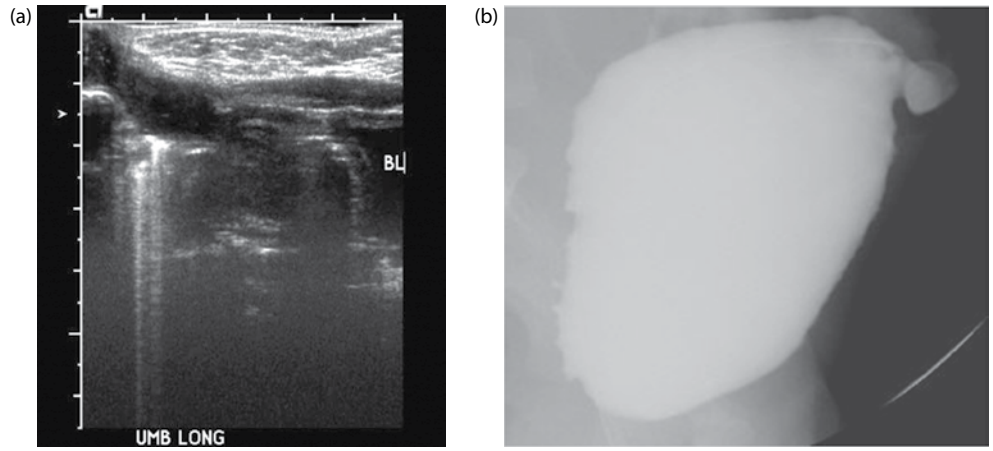


FIGURE 50.7 Imaging in a 1-month-old male with a moist umbilicus. (a) The ultrasound shows a well-defined tract from the umbilicus down to the dome of the bladder (BL). The tract expanded during a bladder contraction (real-time imaging), documenting a communication with the bladder. (b) Catheterization through the tract with a 3.5 Fr feeding tube and instillation of contrast confirm communication with the bladder.

FIGURE 50.8 This is a 14-year-old male with lower abdominal pain, pyuria, and an infected urachus. CT shows an inhomogeneous mass (a) cephalad to the bladder (bl). Anterior bladder wall inflammation and thickening can be seen.

The diagnosis can be made by ultrasound. CT may be useful in defining the extent of the cyst and evaluation of adjacent structures (Figure 50.8).

A urachal diverticulum is often an incidental finding on a VCUG that does not require treatment. A large diverticulum is commonly identified in prune belly syndrome and rarely may require excision if it is a source of significant urinary stasis (Figure 50.9).

BLADDER DIVERTICULUM

A bladder diverticulum is the result of a weakening in the muscular layer of the bladder wall. This may be congenital, but it can be acquired in the presence of bladder outlet obstruction or dysfunctional voiding. In children, the diverticulum is most commonly periureteral. Diverticula are most commonly identified during the evaluation of urinary tract infections, and they may theoretically be a significant source of urinary stasis. The fluid-filled extravesical structure identified on ultrasound is definitively differentiated from a dilated ureter on a VCUG (Figure 50.10). The oblique bladder views localize the location of the diverticulum and whether it is broad based.

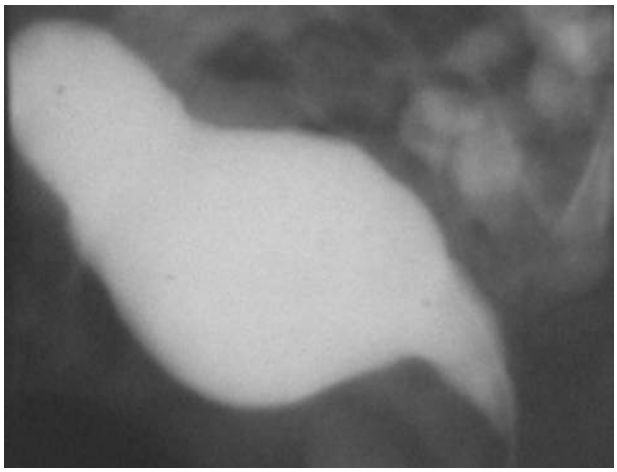
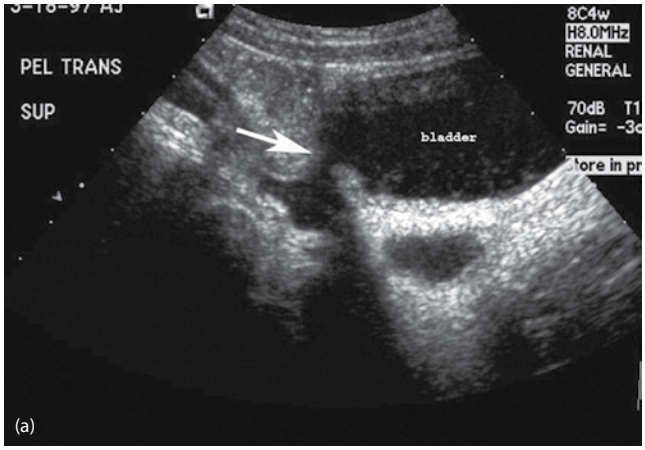


FIGURE 50.9 VCUG in a boy with prune belly syndrome. A wide-mouthed urachal diverticulum is evident. The open bladder neck and tapering distal to the prostatic urethra are typical of prune belly syndrome.

BLADDER MASSES

Bladder masses are distinctly unusual in children. Presenting symptoms are usually related to outflow obstruction (strangury). Occasionally, gross hematuria is identified by the parents, but most children with gross hematuria have no identifiable anatomic abnormality and have a nephrologic source of bleeding. Ultrasound is the initial test of choice in children because it is noninvasive and will usually identify an intravesical or infravesical abnormality. If



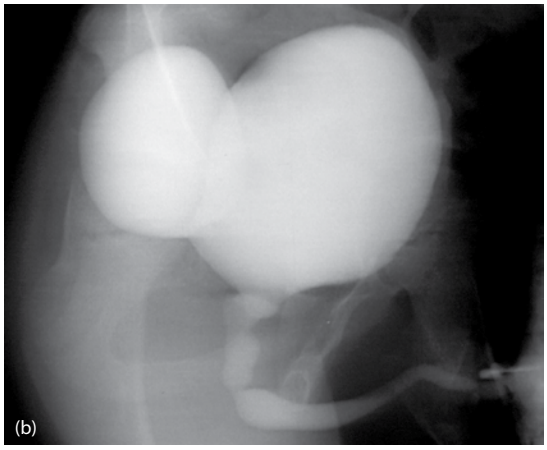


FIGURE 50.10 This bladder diverticulum was identified in a 7-year-old male with recurrent staphylococcal cystitis. On ultrasound (a), it is evident that the tubular structure does not extend cephalad and is not a ureter. The arrow delineates the connection between the bladder and diverticulum. On a VCUG (b), the lateral view confirms an origin low on the bladder base consistent with a congenital periureteral diverticulum.

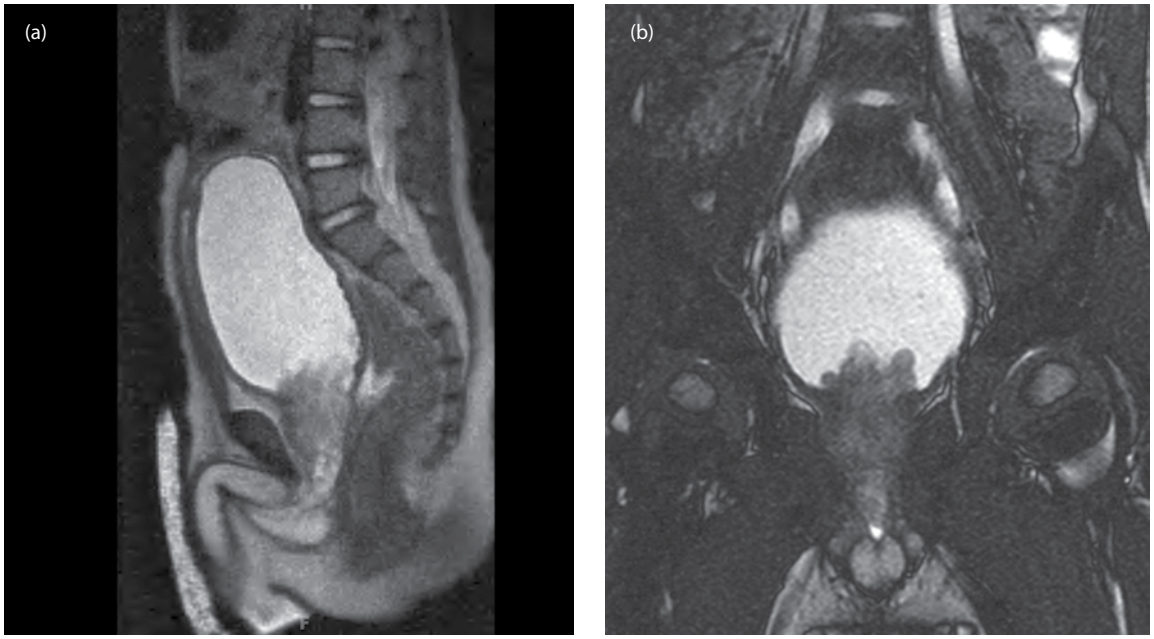


FIGURE 50.11 Rhabdomyosarcoma detected during evaluation of strangury. Ultrasound showed a bladder mass. Sagittal (a) and coronal (b) imaging shows a prostatic-based tumor. There is no definite evidence of extraprostatic extension.

an abnormality is identified, then cross-sectional imaging is usually obtained, although in some clinical situations, an endoscopic evaluation is the next best step.

Rhabdomyosarcoma is the most common bladder malignancy in children. Most present with obstruction and a palpably distended bladder and/or lower abdominal mass. An ultrasound usually reveals a mass at the base of the bladder. MRI offers the best detail in relation to other pelvic organs and is the preferred study for radiologic staging (local and metastatic) (Figure 50.11).

Transitional cell carcinomas of the bladder and fibroepithelial polyps are very rare in children. They are usually well visualized on ultrasound because they usually have a narrow stalk and project into the lumen of the bladder (Figure 50.12).

BLADDER CALCULI

Historically, bladder calculi were related to dietary intake. However, stones are now identified in up to 50% of children after bladder augmentation.[7] They are often identified during routine follow-up imaging but are sometimes associated with hematuria, bladder pain, or urinary infections. On sonography, stones are echogenic foci with associated shadowing (Figure 50.13). Stones

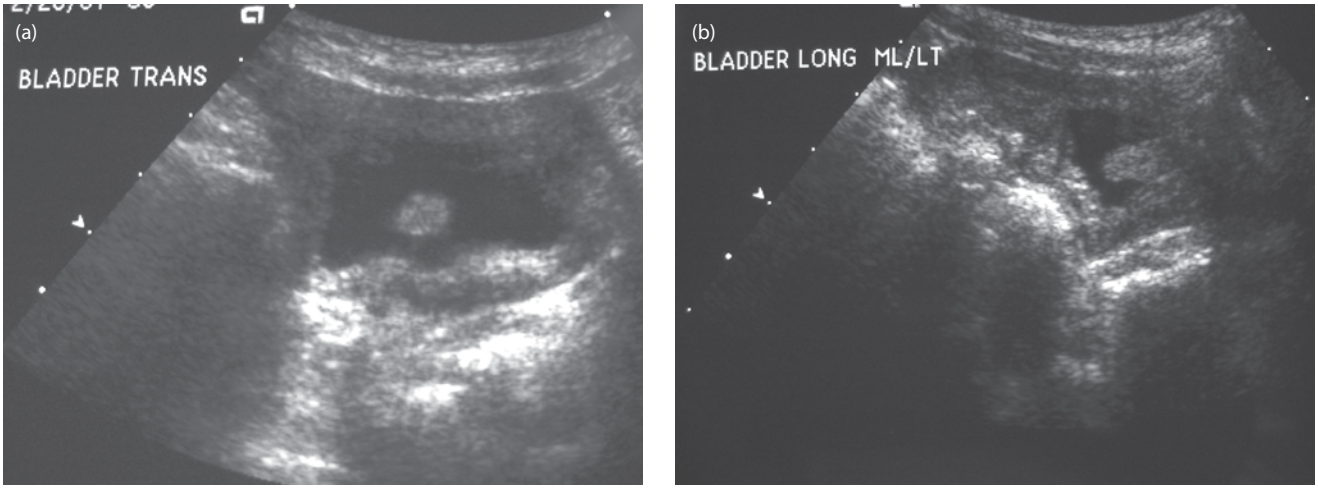


FIGURE 50.12 A fibroepithelial polyp identified in a 2-year-old male with intermittent urinary retention. Transverse views (a) show a "free-floating" mass that extends across the bladder neck on longitudinal views (b) of the bladder. The bladder wall is thickened, consistent with intermittent obstruction.

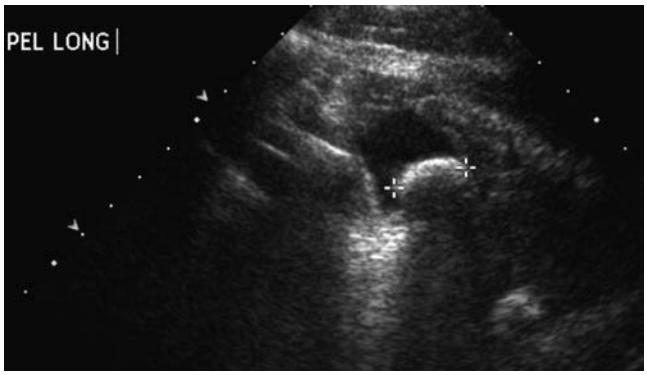


FIGURE 50.13 Bladder calculus in an augmented bladder. A curvilinear shadowing defect is evident on the bladder base.

are usually mobile on the dependent portion of the bladder. Moving the patient into a lateral decubitus position will confirm movement. Images are better if the bladder is partly distended since stones may be in some mucosal folds and confused with echogenic stool that is often present in the true pelvis of these children. A kidney, ureter, and bladder (KUB) helps define the number of calculi.

While ultrasound is not the best imaging study for upper tract stones, it can be useful in the evaluation of distal ureteral calculi that are not readily apparent on plain films. A dilated distal ureter is easily visualized behind the bladder, and a shadowing and echogenic focus at the ureterovesical junction confirm the presence of a stone. If the ureter is not dilated or the stone is proximal to the bladder, ultrasound is usually not useful.

BLADDER RUPTURE

Bladder perforation may occur with blunt abdominal trauma and/or pelvic fractures. Children with a history of bladder augmentation may have spontaneous perforation in the absence of any identifiable trauma. A high index of suspicion is required in the evaluation of children with a history of bladder augmentation and abdominal pain. A VCUG is diagnostic in most cases, but a thorough technique, including postdrainage films, is required to identify smaller perforations. The irregularities normally present in the augmented bladder increase the chance of a false-negative study, and CT scan improves the diagnostic accuracy. Passive bladder distension is inadequate. Retrograde distension with diluted (4%–5%) contrast is necessary to appropriately evaluate for perforation using CT cystography (Figure 50.14).[8] A CT cystogram should be obtained when a perforation is suspected and a VCUG is normal.

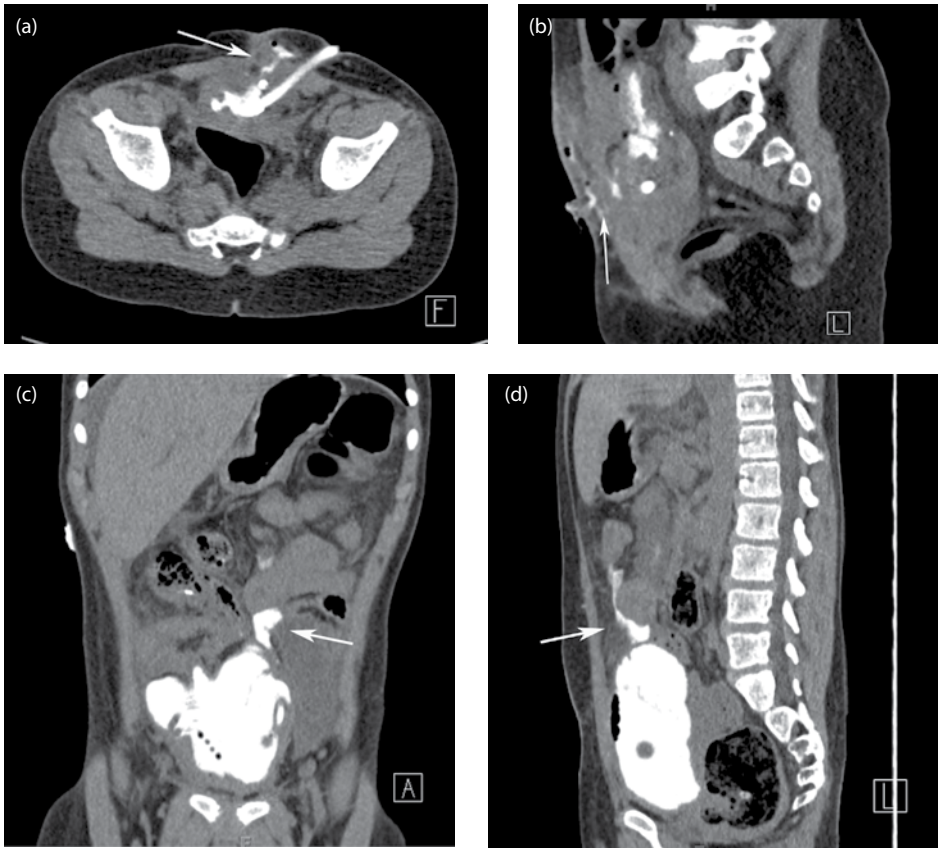


FIGURE 50.14 An extraperitoneal bladder perforation is demonstrated 1 week after augmentation cystoplasty in a patient with bladder exstrophy (a and b). A spontaneous intraperitoneal bladder perforation after augmentation cystoplasty is demonstrated by contrast that outlines the intestines (c and d).

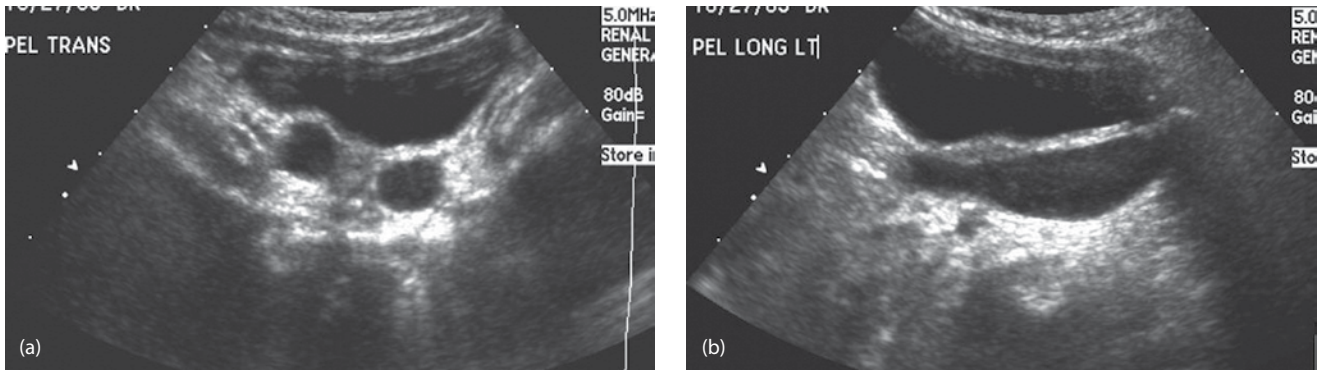


FIGURE 50.15 Bladder ultrasound in a female with recurrent febrile urinary tract infections. Transverse views (a) reveals dilation of distal ureters bilaterally. A longitudinal view (b) shows the dilated ureter coursing distal to the bladder neck. The child had bilateral duplications with upper-pole ectopia.

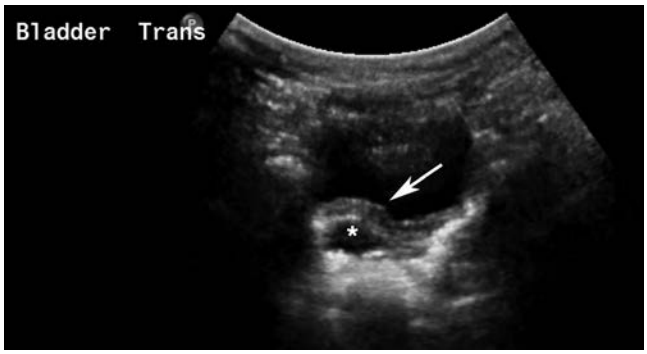


FIGURE 50.16 Pseudoureterocele. A dilated ureter (asterisk) deforms the bladder base. The ureteral wall is very thin compared with the bladder wall (arrow).

URETERAL ABNORMALITIES

Anomalies of the distal ureter are frequently identified during bladder imaging. The normal ureter should not be visualized on ultrasound imaging. When a dilated ureter is identified, it may be indicative of urethral, bladder, or ureterovesical junction pathology.

Megaureter is a generic term applied to an enlarged ureter. Ultrasound easily identifies the presence of these dilated ureters (Figure 50.15). A megaureter can be obstructed or nonobstructed, and refluxing or nonrefluxing. While ultrasound identifies the dilation, a VCUG and renal scintigraphy are required to classify the megaureter.

Ectopic insertion of the ureter occurs most commonly in the setting of renal duplication. The duplication is usually easily identified on ultrasound evaluation of the upper tract because the lower pole of the kidney is not associated with a dilated ureter. Longitudinal ultrasonic bladder views frequently demonstrate a ureteral insertion distal to the bladder neck. Occasionally, the dilated ureter deforms the posterior bladder wall and can be confused with a ureterocele. This pseudoureterocele can be differentiated by noting that the anterior aspect is the same thickness as the rest of the bladder wall, as opposed to the thin, typically imperceptible ureteral wall (Figure 50.16).[9]

Ureteroceles are cystic dilations of the intravesical segment of the ureter. Ureteroceles have a unique appearance

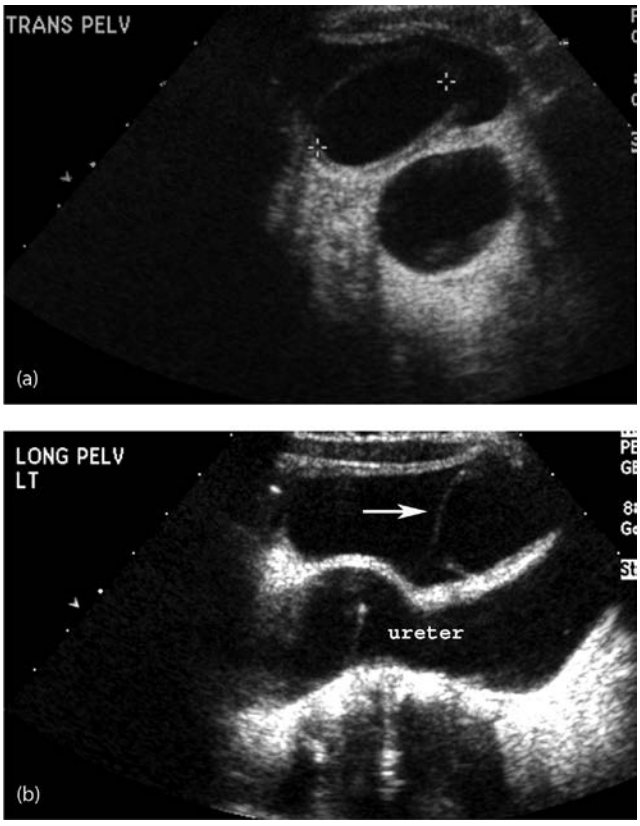


FIGURE 50.17 Bladder ultrasound images in an infant show a thin-walled cystic mass in the bladder, as demonstrated by the calipers. On this random view (a) after a recent void, the ureterocele takes up most of the bladder. A longitudinal views (b) show the dilated ureter associated with the ureterocele (arrow).

on ultrasound. They are thin-walled cystic masses at the bladder base (Figure 50.17). These are usually simple, but are occasionally bilobed or lobulated. In the presence of infection, they may contain echogenic debris. Occasionally, a large ureterocele is not identified if the child has just voided because the apparent bladder urine is actually within the ureterocele, with no urine outside the ureterocele in the bladder. Ureteroceles are usually associated with a dilated ureter posterior to the bladder wall. Intravenous urography and cystography usually reveal a

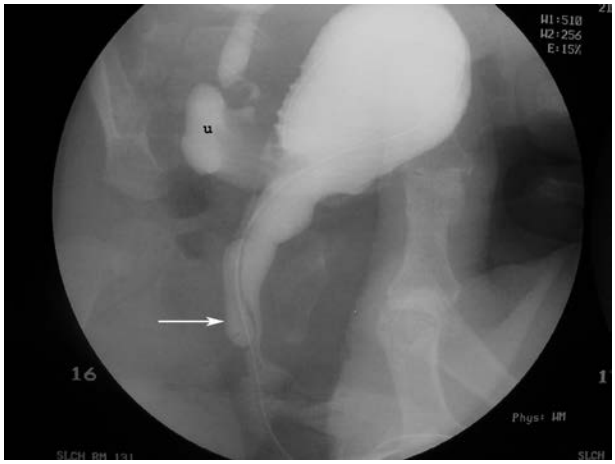


FIGURE 50.18 Cystogram in a female with a ureterocele. A tongue-lie extension is demonstrated on the voiding views (arrow). The ureterocele (u) everts during voiding because of the muscular deficiency in the right hemitrigone.

nonopacified filling defect in the bladder. There may be a significant detrusor defect, and the ureterocele often everts during bladder filling on a VCUG, resembling a diverticulum (Figure 50.18).[10]

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CHAPTER
51

Urodynamics of the Lower Urinary Tract

William E. Kaplan and Edward Gong

INTRODUCTION

The pediatric urologist manages myriad diseases that lead to urinary tract dysfunction. While noninvasive testing is preferred for assessment of urinary tract function, invasive urodynamic studies can provide useful information and should be judiciously utilized. Patients with neurogenic bladder, particularly those who may require surgery for bladder problems, most often require invasive urodynamic testing for appropriate decision-making.

Most children referred for urodynamic studies already have a specific pathologic diagnosis (spinal dysraphism, spinal cord injury, cerebral pathology, etc.) but require a more definitive neurologic classification for appropriate therapy. Many patients with voiding dysfunction require urodynamics to determine whether their urinary problems are neurologic or functional in origin. In addition, patients are referred for urodynamics when other diagnostic studies, such as radiography, are equivocal.

The expansion of pediatric urodynamics in the late 1970s and early 1980s came about because of the need to understand the volume–pressure relationships of the urinary tract. The introduction of clean intermittent catheterization in the 1970s[1] opened the creative gates for the management of children with dysfunctional storing and emptying of their urinary tracts. However, correct characterization of the pathology by urodynamics was critical.

Adult diagnostic techniques needed modification for children, and what began with work on flow rates by Gierup et al.[2] progressed to sophisticated flow and electromyographic studies by Blaivas et al.,[3] and to the introduction of surface monitoring of the pelvic floor by Maizels and Firlit.[4] An additional valuable contribution of correct filling rates by Joseph in 1992,[5] and sedation techniques, emphasized the importance of a more focused approach for children.

This chapter focuses on pediatric urodynamic studies that best categorize neurologic and nonneurologic bladder pathology and help to define the best treatment modalities.

INDICATIONS FOR URODYNAMIC STUDY

Evaluation and characterization of bladder dysfunction in neurogenic bladder disease (NBD) is the most accepted indication for urodynamic evaluation in children. Early and repeat evaluation of children with NBD has helped identify children at high risk for urinary tract deterioration.[6] Medical and surgical management of patients with NBD has been guided by urodynamic evaluation in addition to clinical symptoms and radiographic imaging. Initial urodynamic studies performed on a neonate have proven beneficial in preventing bladder deterioration. Repeat urodynamic evaluation should occur with clinical changes, such as new-onset hydronephrosis, increase in incontinence, recurrent urinary tract infections (UTIs), voiding changes, or increase in postvoid residual.

While NBD is the most accepted usage for urodynamic study, children suffering from nonneurogenic bladder disease (NNBD) can also potentially benefit from urodynamic studies. Patients with failed initial treatment for NNBD have been shown to have a high frequency of pathological findings on urodynamic studies, which has led to alteration of the treatment strategy based on urodynamic findings.[7]

Finally, children with anatomic bladder dysfunction, such as posterior urethral valves (PUVs), anorectal malformations, or bladder and cloacal exstrophy, may potentially benefit from urodynamic evaluation. Patients with PUVs may benefit from early urodynamic studies. Casey et al. demonstrated that PUV patients with early initial urodynamic studies that demonstrated high voiding pressures or small capacity benefited from early initiation of anticholinergic medications.[8] Furthermore, proper long-term urodynamic assessment may assist in medical and surgical management of children with evolving bladder disease with PUVs.[9]

MEDICAL HISTORY

Urodynamic studies should be an adjunct to good clinical practice. A thorough history and physical examination must precede any diagnostic study, a consideration placed on the clinical response that the study will drive (Table 51.1). In patients in whom the diagnosis is clear, e.g., spinal cord injury or myelomeningocele, eliciting a diagnosis is not usually the challenge. However, determining the best management to maintain continence and prevent renal deterioration can be exceedingly elusive. Furthermore, patients with urinary tract dysfunction with no obvious neurologic abnormality will challenge the diagnostic skill of even the most experienced pediatric urologist.

TABLE 51.1 Evaluation of children who wet

History	Prenatal, congenital history Voiding characteristics Bladder and bowel function
Physical examination	Abdomen and perineum Spine Lower extremities: Reflexes Gait Physical structure
Laboratory	Urinalysis/culture Chemistry: urine/serum
Radiography	Ultrasonography: renal/bladder Voiding cystography Flat plate abdomen/spine (AP and lateral)
Urodynamics	Flow/bladder capacity Cystometry Pelvic muscle evaluation: pads/needle Compliance: LPP/VLPP and PSBV

Abbreviations: AP, anteroposterior; LPP, leak point pressure; VLPP, Valsalva leak point pressure; PSBV, pressure-specific bladder volume.

An accurate voiding history is most important. The patient's age and expectations of urinary control may dictate the concerns about voiding habits. However, even in infants, the pattern of wet and dry diapers may be important to discovering the diagnosis. Newborns with constant dribbling or signs of overflow incontinence may have undergone a traumatic delivery, e.g., hyperextension injury to the cervical spinal cord.

Infants of diabetic mothers have an increased risk of neural tube defects. Infants of mothers with substance abuse are at increased risk for hydronephrosis. These are only a few examples that illustrate the importance of a thorough prenatal and obstetric history before scheduling and tailoring the type of urodynamics study.[10–12] Historic information, such as prematurity or global delay in physical or mental capabilities, is important. Although this information may not aid in therapy, it may help to explain to parents how delays in gaining urinary control occur. Infants with irregular bowel habits (diarrhea or constipation), in association with urinary symptomatology, should prompt careful evaluation.

As the child matures, incontinence or UTIs may become the primary symptoms. A thorough voiding history should be elicited from the child and his or her parents. It is important to engage the child, as often parents are not aware of a school-aged child's voiding and bowel elimination history when they are not at home. Frequency of wetting, voiding characteristics, presence of urgency, quality of the flow rate, and whether a child is wet are important historic features. The boy with a poor flow rate would be suspicious for having anatomic bladder outlet obstruction, whereas the girl with paradoxical incontinence (continuously damp while voiding normally) might have an ectopic ureter. In the older child, the history must include details on bowel habits, because it is clear that constipation has a direct relationship to urinary control, as well as urinary infections.[13,14]

A clear history of symptoms associated with UTI is necessary to adequately determine the need for urodynamic or other testing. The clinician should determine if the UTIs were symptomatic or associated with fevers. The collection method (voided or catheterized) for previous cultures should be ascertained. Previous culture results should be viewed and attention paid to the type of organism, resistance patterns, and colony counts.

It is exceedingly important to take a thorough bowel elimination history. Multiple studies have shown the correlation between constipation or "stool retention" and urinary symptoms. Bowel symptoms have been found in up to half of patients with voiding dysfunction.[15] Management of bowel symptoms is necessary in the treatment of children with voiding dysfunction. Rectal distention has been shown to negatively affect bladder capacity, sensation, and overactivity[16] and can potentially cloud urodynamic results. A medication list should be reviewed, as many medications can have effects on bladder contractility, as well as bowel movements.

The use of a voiding diary or 12 h home pad test may also be helpful.[17,18] However, in practice, the clinician may easily misinterpret the results if less than fastidious notes are kept, or if the pads are not changed promptly. Another potential tool to assist in the clinical evaluation of patients with voiding dysfunction is validated measures that allow for longitudinal follow-up of lower urinary tract symptoms. Several validated tools have been developed with good correlation with clinical impression of severity of disease;[19] however, significant work remains on the utility of these instruments regarding long-term management outcomes and correlation with the necessity of urodynamic testing.

PHYSICAL EXAMINATION

Before planning a urodynamic study, a thorough physical examination is essential. Children may exhibit evidence of delayed gross motor development or abnormal fine motor skills consistent with global abnormalities from in utero or birthing issues. In these children, a complete neurologic examination by a pediatric neurologist, including muscle tests and nerve conduction velocity, may be indicated.

A routine systematic approach, including having the child completely undressed from head to toe (although covered with a warm blanket and with a nurse and parent in attendance), will help to reveal general congenital defects that might contribute to syndromes that involve the urinary tract. Following the general assessment, most of the pertinent pathology is found below the umbilicus. The abdomen should be palpated for stool, although significant fecal retention can exist with a soft abdomen and an empty rectal vault.

The back, perineum, and lower extremities should be examined critically. During examination of the back, all midline abnormalities should be cause for concern. However, there is less importance if a simple dimple can be grasped with the tip of the coccyx. Obvious or subtle midline skin tags, tufts of hair, or vascular malformations may indicate underlying spinal malformations, e.g., lipomas, and spinal magnetic resonance imaging (MRI) is then indicated, though spinal ultrasound is preferred in infants prior to ossification of the vertebral bodies. A short or abnormal gluteal cleft may indicate an underlying

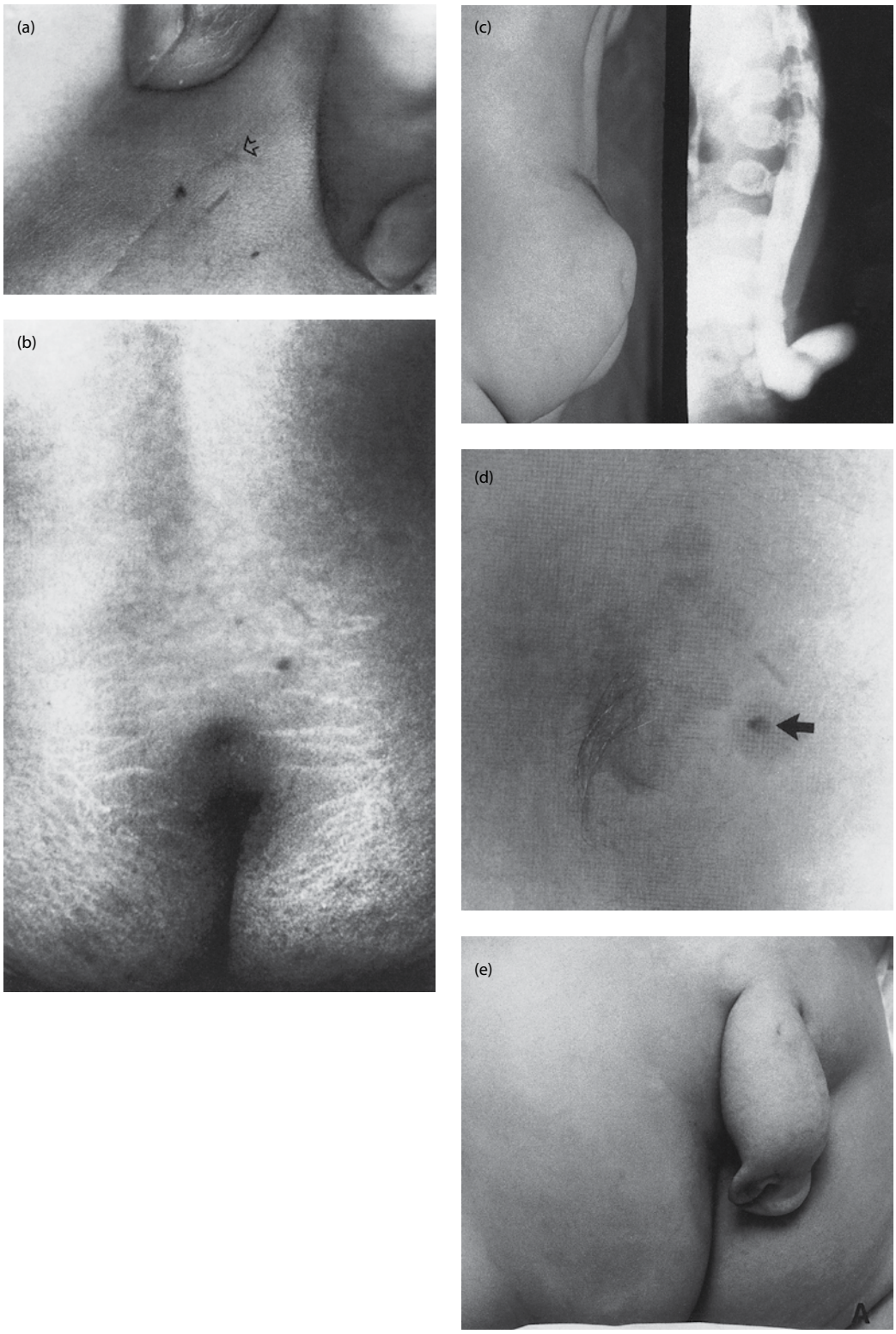

FIGURE 51.1 Cutaneous lesions discovered on midline spinal examination: (a) dermal sinus tract (open arrow) in infant who developed meningitis shortly after birth; (b) a subtle fullness of one buttock and mild scoliosis in a child with incontinence and subsequently discovered to have a lipoma; (c) an obvious sinus tract and lipoma in infant with lipomeningocele; (d) a sinus (arrow) and associated hairy patch characteristically associated with a flat capillary hemangioma; (e) an unusual appendage and dermal sinus tract.

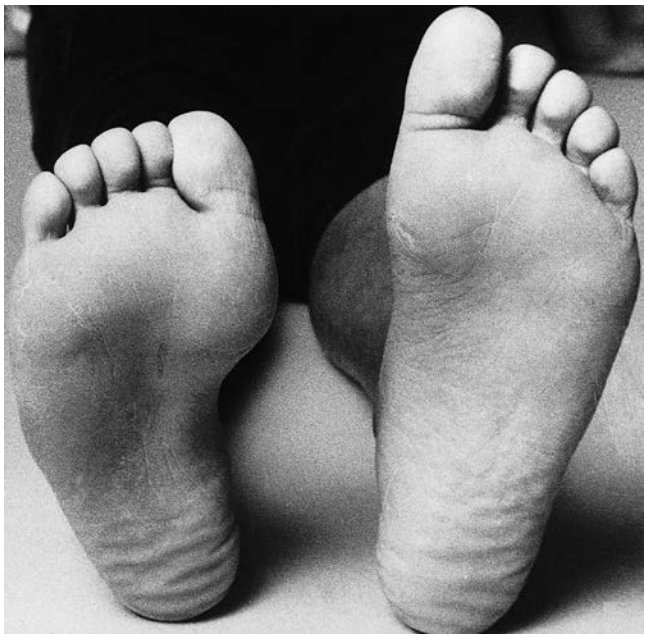

FIGURE 51.2 Leg length and foot asymmetry in a 10-year-old child with spina bifida.

sacral dysgenesis or agenesis. A flattened buttock suggests deficient gluteal muscle tone, consistent with an anorectal malformation or caudal regression syndrome (Figure 51.1).

A neurologic examination, including rectal tone, perianal sensation, and the presence or absence of a bulbocavernosus reflex, should be noted. A digital rectal examination confirms the presence of stool and rules out rare prostatic lesions. The vaginal introitus should be inspected to rule out significant labial adherence or urethrovaginal abnormalities. In the boy, the meatus should be observed and, if uncircumcised, the foreskin either retracted gently or pulled forward, so that the meatus can be inspected through the tunnel of foreskin.

The lower musculoskeletal system should be examined, and any discrepancy in muscle tone or muscle mass should be noted. It is essential to remove the shoes and socks to discover a high-arched foot or hammer claw digits, consistent with a true neurologic abnormality (Figure 51.2). A gait disturbance is noted easily in barefoot children as they walk up and down the corridor. Finally, the deep tendon reflexes should be evaluated. Exaggerated reflexes are consistent with cerebral palsy.

OFFICE-BASED TESTING

At the first office visit, a urinalysis (glucose and specific gravity) and urine culture should be obtained. Children with NBD should also undergo renal bladder ultrasound to evaluate for hydronephrosis. In children who void, this can be beneficial in determining a postvoid residual. Boys with daytime wetting should also undergo renal bladder ultrasonography to evaluate for potential PUVs. All children with febrile or recurrent UTIs should have a renal bladder ultrasound performed as well. In children with a normal renal or bladder sonogram, and no history of significant UTIs, the majority of patients will be started on a timed voiding program, with attention to bowel habits. Pharmacologic therapy, such as anticholinergic medications, is typically not considered as a first-line therapy in children with nonneurologic voiding dysfunction. In the remaining patients, a more thorough workup, including radiographic evaluation with a voiding cystourethrogram (VCUG) and urodynamic studies, is indicated.

RADIOGRAPHIC EVALUATION

Radiographic examination is used selectively. Older children with daytime wetting will undergo a renal and bladder sonogram with postvoid imaging to evaluate bladder emptying and the effects of bladder fullness on upper tract dilatation. Alternatively, if an in-office bladder scanner is available, then bladder scan postvoid residual is sufficient. If UTIs are an issue, a conventional x-ray VCUG is performed to evaluate the bladder, outlet, and urethra. This study can also document whether there is significant stool in the colon. If a VCUG is not performed, but concern exists for stool retention, a kidney, ureter, and bladder (KUB) will be obtained to evaluate stool pattern. Specific characteristics on KUB have been associated with a greater risk of lower urinary tract symptoms.[20] KUB can also be useful to assess the lower spine for bony abnormalities. Children with both fecal and urinary incontinence should have dedicated lumbosacral images. Prior to ossification of the spine, infants can be evaluated with spinal ultrasound with excellent accuracy. In patients with clearly abnormal studies, spinal MRI is performed (Figure 51.3).

FIGURE 51.3 Lumbosacral MRI. T1-weighted image indicates a long tethered spinal cord. The elongated (bowstring) cord ends in the lipoma rather than at L3.

LOWER URINARY TRACT URODYNAMICS

Lower urinary tract urodynamic studies in children include both noninvasive and invasive components. Noninvasive testing includes uroflowmetry with or without electromyography, and with or without bladder scan postvoid residual. Invasive testing includes cystometry and pressure flow studies. In the majority of cases, the child with a nonneurogenic voiding abnormality will be old enough to cooperate, tolerating a precystometrogram flow study, followed by a cystometrogram with patch electrodes and a postvoid study. Typically, the child with neurogenic disease comes to the laboratory on a clean intermittent catheterization program and is being evaluated because of increasing dysfunction (tethered cord and shunt malfunction). Voiding studies become less important, and a needle electrode electromyogram (EMG) may be more important. In all instances, a relatively clean rectum will result in a more accurate study.

NONINVASIVE URODYNAMIC STUDIES

The urinary flow rate measurement is a simple noninvasive study that is defined as the voided volume per unit time (mL/s) (Figures 51.4 and 51.5, Table 51.2).[21] This study can evaluate incontinence secondary to problems in storage or emptying. In combination with patch electromyography and bladder scan post void residual, uroflowmetry can be a powerful tool to evaluate voiding dysfunction in children. For children without evidence of neurogenic bladder, uroflowmetry with a EMG and post void residual urine (PVR) can often suffice, and invasive urodynamic studies avoided in a sensate child. Our approach to uroflowmetry with a EMG is similar to that described by Van Batavia et al.[22] Based off of a new classification system introduced by Glassberg et al.,[23] Van Batavia et al. described management of four conditions that can be identified from uroflowmetry with a EMG without the use of cystometry. The new uroflowmetry-derived conditions are as follows: dysfunctional voiding (DV), idiopathic detrusor overactivity disorder (IDOD), detrusor underutilization disorder (DUD), and primary bladder neck dysfunction (PBND). DV is characterized by pelvic floor activity during voiding with or without a staccato voiding pattern. IDOD is identified by a quiet EMG during voiding, but a shortened lag time (<2 s). DUD patients will have a voided volume above the estimated bladder capacity for age with a quiet pelvic floor during voiding with a normal flow curve. PBND is identified by hesitancy with a delayed lag time and quiet pelvic floor activity during voiding with a right-shifted flow curve.[23] These terms are derived from the International Continence Society and International Children's Continence Society (ICCS) guidelines,[24,25] but specific ICCS terminology is not appropriate, as ICCS terminology requires cystometrogram data. Children with DV during voiding are referred to biofeedback, children with IDOD may be started on anticholinergic medications, children with PBND may be started on alpha-blockade, and children with a large bladder capacity and quiet pelvic floor activity are treated with timed voiding. Stool retention management is paramount in all children.

The reliability of uroflowmetry comes from repeated studies (at least two) and is related to voided volume. Bladder capacity (BC) should be based on age rather than body surface. Although the linear formula of Berger et al.[26] and Koff,[27]

$$\text{BC(ounces)} = \text{Age} + 2$$

has been the most frequently used to estimate bladder capacity, it is clear that bladder growth from a newborn (especially in the first years) to 13 years is not linear. Kaefer et al.[28] responded to the challenge of modifying this equation with their nonlinear equation:

$$2 \times \text{Age (years)} + 2 = \text{Capacity (ounces) for children} < 2 \text{ years old and}$$

$$(\text{Age (years)} / 2) + 6 = \text{Capacity (ounces) for children} \geq 2 \text{ years old}$$

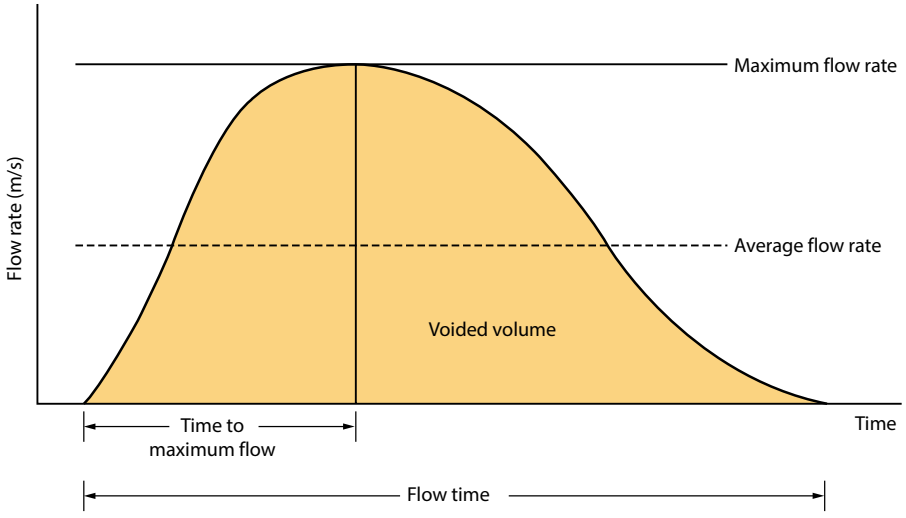

FIGURE 51.4 Idealized diagram of urine flow. (Modified from Blaivas J, Chancellor M eds. *Atlas of Urodynamics*. Baltimore: Williams and Wilkins, 1996. With permission.)

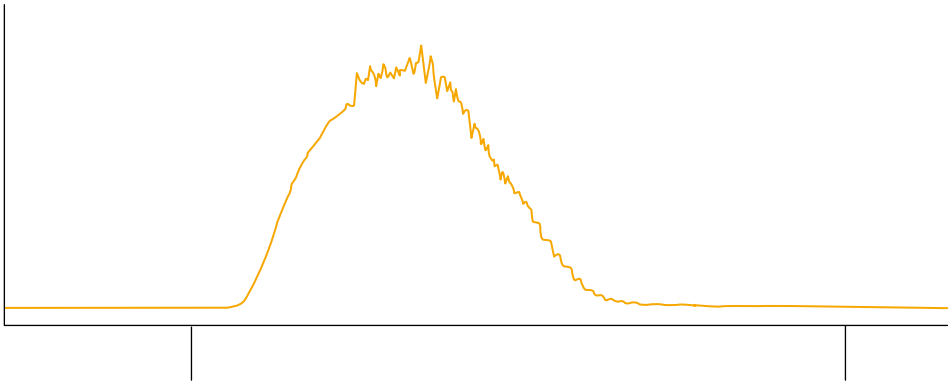

FIGURE 51.5 Normal uroflow in a 12-year-old male: maximum = 38 mL/s, average = 17 ml/s, volume = 222 mL.

TABLE 51.2 Urodynamic studies

Urodynamic study	Purpose: to evaluate:
Uroflow/residual urine	Voiding function sensation, storage, emptying of the bladder
Cystometry	Coordination/function of muscular outlet
Pelvic floor/external sphincter EMG	Bladder/outlet function
Leak point pressure: Bladder Stress (VLPP)	Storage pressure Competence of bladder neck/proximal urethra
Videourodynamics	Anatomy and function of bladder and outlet (simultaneously)

Abbreviations: EMG, electromyogram; VLPP, Valsalva leak point pressure.

In all these studies, data were based on findings in normal children. Children of <14 years of age with spina bifida and neuropathic bladders do not exhibit growth rates similar to those of normal children. In fact, on comparing bladder growth in a small group of patients with spina bifida to the linear formula of Berger, bladders of patients with spina bifida grew half as well as those without neurologic abnormalities. To calculate bladder capacity in children with myelodysplasia, the formula 24.5 × Age (years) + 62 can be utilized.[29]

Thus, in order to calculate normal flow patterns and rates, one must first know the expected bladder capacity in order to determine whether the voided volume is within the expected range. Prevoid bladder volume is measured with a bladder scanner. Accurate determination of the flow rate/voided volume is a common problem, particularly in the anxious child or in the child who voids frequently in small volumes. In general, voided volumes of <50% expected capacity should be suspect.[30,31] We recommend filling the bladder by forcing oral fluids on the way into the laboratory or by intravenous hydration. Multiple voids can be spontaneous, but furosemide administration can be helpful to ensure repeated measurements.

The most important feature of the uroflowmetry study is the shape of the curve. In a study of 180 schoolchildren aged 7–16 years, 98% had a bell-shaped flow pattern (Figure 51.4).[30] The shape of the curve had no relationship to voided volume, but the other parameters were volume dependent. Although the maximum flow and average flow can be of diagnostic interest, the shape of the flow appears to be the best screening parameter. Repeated deviations from the bell-shaped curve should prompt further studies (Figure 51.6). EMG lag time can be beneficial in determining patients with bladder overactivity (short) or PBND (long) and has been correlated with urodynamic studies.[32]

Estimation of residual urine can be an important clue to overall bladder function. Except in infants, the child's bladder should empty to completion with each void. There are multiple pitfalls when evaluating for retained urine. An anxious child in a foreign setting will not void efficiently. Furthermore, children with significant reflux may often harbor residual urine just after voiding. Thus, whereas complete evacuation can be helpful to know, an elevated postvoid residual may not signify important pathology. A bladder scan with ultrasound or placement of a catheter just prior to the cystometrogram will determine the residual urine.

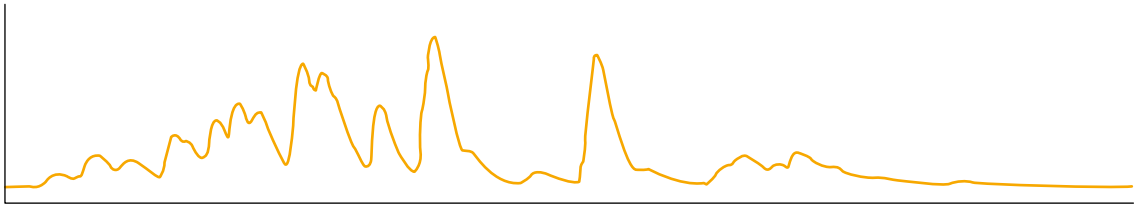

FIGURE 51.6 Abnormal uroflow in an 8-year-old male with abdominal straining and no detrusor activity.

INVASIVE URODYNAMIC STUDIES

Setup

It is most important that the child is comfortable, and that the laboratory is child-friendly (posters, movies, tablet computers, books, stickers, etc.) and temperature controlled. All voidings should be as private as possible. For the older child, a separate room with a flowmeter and a one-way mirror to observe voidings can be helpful. Given enough time and patience, most studies can be completed successfully with reproducible results. We utilize child life experts at our institution to alleviate anxiety in children based off of data extrapolated from the utilization of child life experts for a VCUG.[33] Rarely, an extremely anxious child will require sedation for urodynamic studies. However, studies have demonstrated that utility can still be derived from urodynamic studies in which children have received ketamine or midazolam.

The urodynamic portion of videourodynamics is conducted in a routine fashion, by having the child arrive at the urodynamic suite in as relaxed a state as possible. Prestudy rituals include detailed discussions with the family about expectations and methods to alleviate the child's fears during the procedures. A scout film before placement of EMG patches or catheter probes helps to assess bowel status and guides future management of constipation, if present. Severe constipation adversely affects vesicosphincter activity. If the child arrives with a full bladder, we perform a bladder scan and noninvasive flow study with patch electrodes. For the cystometry portion of the examination, the technique is the same, except that the infusant is radiographic contrast. A triple-lumen urethral catheter is slowly withdrawn, and a urethral pressure profile is obtained. We position a radiopaque marker that identifies the urethral port at the point of highest urethral pressure.

Cystometry is the pressure–volume study of the bladder that examines both the filling and storage and the voiding phases of micturition (Figures 51.7 and 51.8). Both

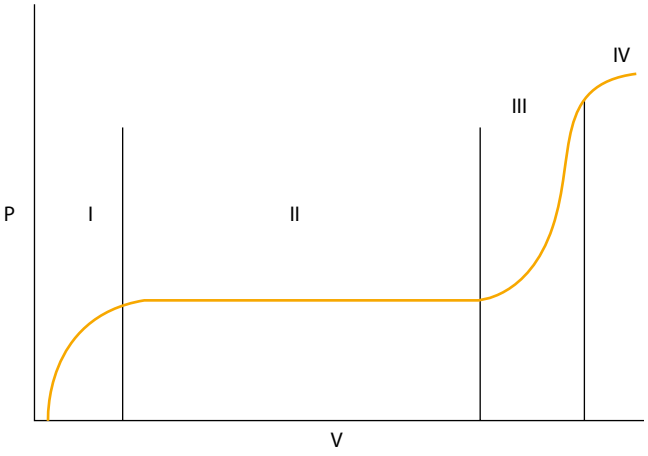

FIGURE 51.7 Cystometrogram indicating four phases and filling and detrusor activity: I, initial vesical pressure with early filling; II, stable tonus limb; III, increase in tonus at full vesicoelastic expansion; IV, voiding; P, pressure; V, volume. (Modified from Dmochowski R. *Urol Clin North Am 1996*;23:243–51. With permission.)

parameters are instrumental in the assessment of bladder health in relationship to upper tract drainage. This can be done with or without videourodynamics. If video is to be utilized, the study can be performed initially with the patient supine on a fluoroscopy table, imaged with a C-arm that eliminates the need for an expensive table, or seated in a multipositional, radiolucent micturition seat. The standing position can help delineate the bladder neck and urethrovaginal component more readily; however, many adolescent and young adult females may not easily initiate a void in the unusual standing position. In the standing position, the right posterior oblique projection provides the best image of the bladder neck. Under fluoroscopic control, the bladder, bladder neck, and urethra are visualized while the pressure is recorded.

Filling Phase and Storage Assessment

An accurate assessment of bladder storage must begin in a calm laboratory setting with the necessary techniques and props to decrease patient anxiety. The technician then passes an age-appropriate catheter. Male newborns can usually accommodate a 6 Fr short pediatric urodynamics catheter. For smaller children, a 5 Fr feeding tube can be connected to a three-way stopcock that allows for both measuring pressure and using fluid instillation. We try to take care to avoid an overly large catheter in newborns, which can obstruct the urethra and produce an abnormally high leak point pressure, as the fluid tries to leak around the catheter.[34] In older children, we use a 7–10 Fr catheter. Latex-free materials are essential for individuals with spina bifida, as they are prone to severe latex allergy and reactions.

Bladder filling is accomplished at 5%–10% of expected bladder capacity.[5] Upon placement of the urodynamics catheter, a prestudy postvoid residual is determined. At least two filling cycles should be performed for urodynamic studies, as the initial filling cycle is often inaccurate due to child anxiety. This is particularly true in the neurologically intact child. We use warm saline from a range of body to room temperature. Joseph[5] noted that a change in detrusor pressure, as well as maximum detrusor pressure, was adversely affected by increasing the rate of filling from slow (approximately 2% of estimated bladder capacity, 0–10 mL/min) to medium (approximately 20% of estimated bladder capacity, 10–100 mL/min) fill. In general, we recommend filling at less than 10 mL/min in children. Filling should continue until the child voids or develops a strong urge to void, or detrusor pressure has exceeded 40 cmH_2O without a void. Otherwise, infusion can continue to more than 150% of the expected capacity or the rate of leakage matches the rate of filling.

During the filling and storage phase, we record both intravesical and abdominal pressures. The abdominal pressure is obtained by inserting a pressure catheter into the rectum. The pressure transducers should be level with the symphysis pubis. The software from the urodynamics system then subtracts the rectal (abdominal) pressure from the intravesical pressure to obtain a true detrusor pressure. Although abdominal pressures are measured, there is no replacement for direct, hands-on, expert observation to determine the effects of straining, crying, and

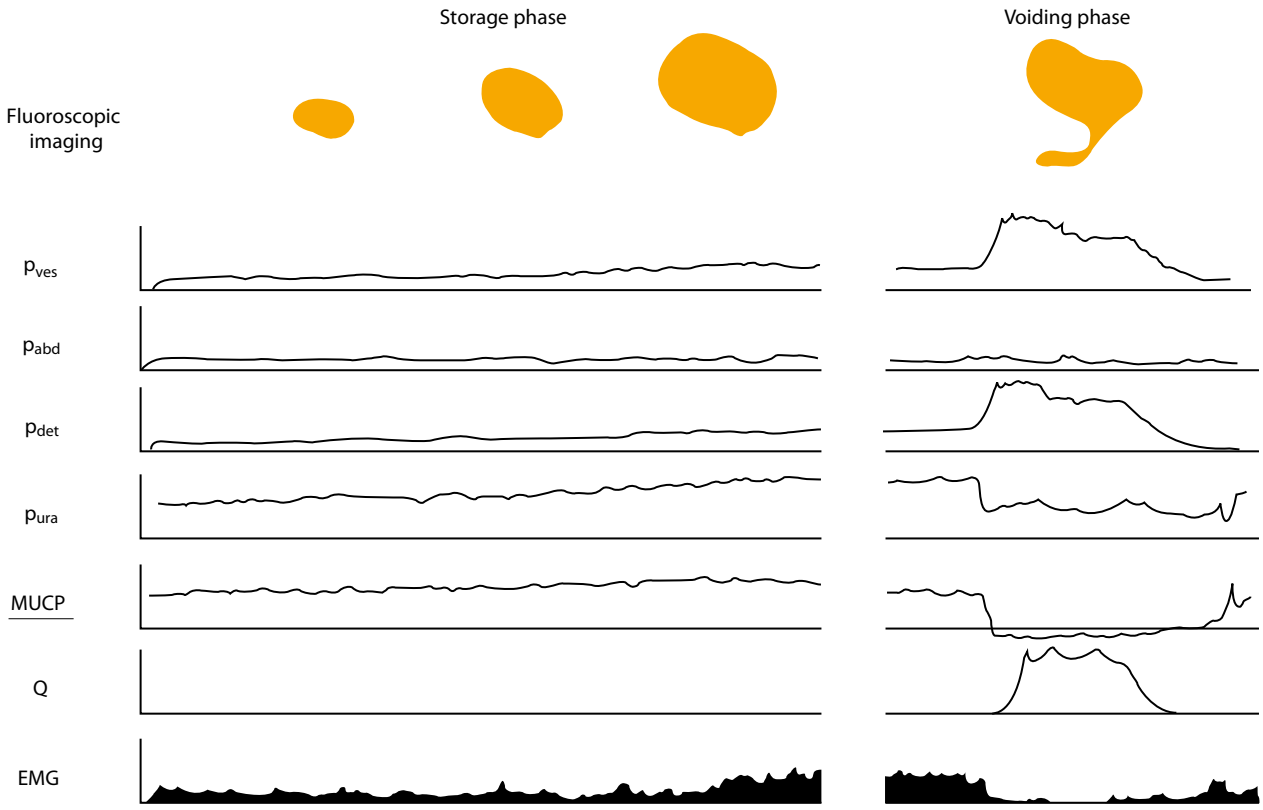

FIGURE 51.8 Idealized urodynamic tracing with accompanying fluoroscopic images. p_{ves} = intravesical pressure; p_{abd} = abdominal pressure; p_{det} = detrusor pressure; i.e., the $p_{ves} - p_{abd}$; p_{ura} = urethral pressure; MUCP = maximal urethral closure pressure; Q = urinary flow; EMG = surface electromyography. (Modified from Abrams P, Khoury S, Wein A. WHO publication. *Incontinence: 1st International Consultation on Incontinence.* Geneva: World Health Organization, 1998, 353–401. With permission.)

gross movements. These should be observed, noted, and accounted for when evaluating urodynamic results.

Valsalva and requests for repeated coughing are utilized to provoke the patient's incontinence symptoms. We examine the bladder base and urethra fluoroscopically for mobility and leakage, respectively. A postvoid residual is calculated and compared with the prestudy noninvasive residual. The videourodynamic study can accurately detect detrusor leak point pressure with straining. The importance of this finding relates to bladder compliance. If the outlet is open fluoroscopically, incontinence occurs with no change in bladder compliance. On the other hand, if the outlet is closed during a detrusor contraction (detrusor sphincter dyssynergia), incontinence may still occur, but only with elevated detrusor pressures (compliance).

Compliance

Since the late 1970s, great advances in pediatric urology have occurred in the field of bladder management. A firm grasp of the importance of bladder health or "safe" compliance became evident coincident with the introduction of clean intermittent catheterization by Lapides. The interest in neurourology blossomed with nonsurgical as well as reconstructive techniques introduced to reconfigure bladder compliance. McGuire et al.[35,36] and Houle et al.[37] described two complementary studies to evaluate lower tract function and health. McGuire et al. popularized the concept of the leak point pressure. The leak point pressure is the detrusor pressure at which leakage occurs through the outlet. It is dependent on the resistance to flow. Without fluoroscopy, the point of resistance will not be evident. It is measured by performing a slow-fill cystometrogram, noting the pressure at which the leak occurs around the catheter per urethra. It has been shown in several centers that in the myelodysplastic population, children with leak point pressures of >40 cmH_2O are at greater risk for upper tract damage (hydronephrosis and reflux) than patients who have leak point pressures of <40 cmH_2O.[37,38] Although many groups base their treatment program on this "magic number" of 40, the limitations of a single leak point pressure are considerable.

Despite its relationship to outlet resistance, measurement of leak point pressure can be misleading when used to evaluate continence capability. Specifically, a high leak point pressure implies a good chance for continence. However, in the myelodysplastic population, the leak point pressure may be high but still not correlate with significant continence in the presence of a fixed but open bladder outlet.

The leak point pressure is an accurate measure of bladder storage pressure. However, Houle et al. proposed that observing the volume at which a child can safely store urine, i.e., pressure-specific bladder volume, might better assess bladder storage characteristics. Houle et al. indicated that in normal children, 99% of bladder capacity

can be stored at <30 cmH_2O. Thus, a safe pressure of 20–30 cmH_2O was chosen and the volume noted that kept the pressure in that range.[35,39] This may be a most useful judge of compliance. Therapeutic interventions can be implemented based on this safe storage pressure. Voiding and catheterization diaries for patients may be obtained, and evacuation schedules or additions of medications (anticholinergics) adjusted accordingly. If conservative measures do not consistently allow the bladder to store in a safe zone, augmentation or neuromodulation procedures are used (Figure 51.9). It seems prudent, and it is easy to obtain the leak point pressures, both simple and stress, as well as the pressure-specific bladder volume. However, it is unclear whether these data alone should be used as a basis to intervene prophylactically or must be interpreted in conjunction with imaging (e.g., renal and bladder sonography). Both programs have their staunch advocates. Accurate studies performed in a consistent and timely manner can only benefit the current population of children and give guidance for future cost-effective management.

The stress leak point pressure measurement was an innovation to help in the assessment of continence capability. The stress leak point pressure is slightly different from the simple bladder leak point pressure and can be determined without fluoroscopy. This value is obtained by slowly filling the bladder and having the child strain as if to have a bowel movement. The lowest pressure is then noted during which leakage first occurs. We ask the child to cough vigorously while the pressure is measured. This marker helps evaluate the capability of the outlet in both the open and the poorly functioning state (e.g., the myelodysplastic child). The stress leak point pressure helps to determine whether outlet reconstructive procedures are needed to achieve urinary continence.[40]

Pressure Flow Studies

In children with intact micturation function, the urodynamic studies are not complete until at least one spontaneous void. Important features to annotate are the opening pressure (the pressure at which micturation begins), which should be low, indicating a collapsed urethra and no evidence of obstruction distal to the bladder neck. Voiding pressures are dependent on sex and age. Boys tend to have a higher voiding pressure than girls, with voiding pressures greater than 100 cmH_2O in boys less than 1 year of age. Girls have voiding pressures from 60 to 70 cmH_2O. By the ages of 1–3 years, boys decrease voiding pressure to 70 cmH_2O, while girls maintain voiding pressures of 60 cmH_2O.[41] Knowing normal voiding pressures is important, as high voiding pressures with normal or low flow rates can be indicative of anatomical or functional bladder outlet obstruction. A concomitant EMG that demonstrates no activity during voiding is particularly worrisome for anatomical obstruction. If the EMG demonstrates

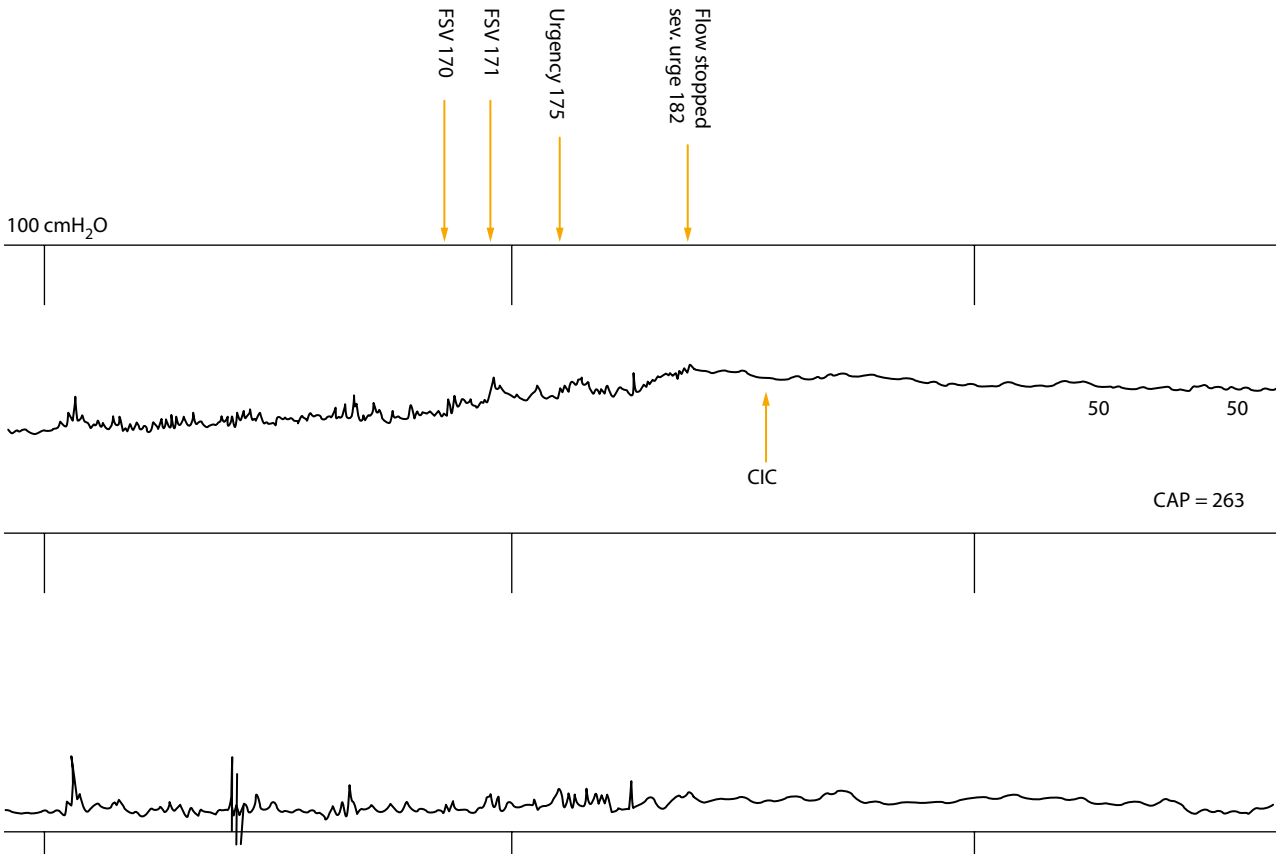

FIGURE 51.9 Urodynamic study to show poorly compliant neuropathic bladder pressure at capacity is 62 cmH_2O and patient-recorded typical catheterization volumes (CIC) that were at elevated pressures (70 cmH_2O). Failure at conservative management resulted in augmentation.

activity, this could be a functional bladder outlet obstruction, such as detrusor sphincter dyssynergia or DV. The shape of the flow curve is the most important feature to determine voiding dysfunction. A staccato voiding pattern can be suggestive of pelvic floor activity during voiding.

An EMG should be performed at the same time as detrusor pressure evaluation. The electrodes can be surface pads, wires, or concentric needles. In children with neurogenic disease and a lack of perineal sensation, we record from the external sphincter or perineal floor using needle electrodes. In boys, we place a concentric needle directly into the bulbocavernosus muscle by aiming toward the bulb of the urethra. For the external sphincter, the needle is placed through the perineal skin just below the bulb of the urethra. A finger in the rectum will help to guide the needle. In females, the external sphincter is identified by a needle placed just lateral to the urethral meatus and advanced <1 cm. To capture individual motor action potentials correctly, both an audio channel and oscilloscope are needed. A trained neurophysiologist best performs this study. This technique is the most accurate method of diagnosing the degree of denervation of the urethral sphincter and establishing the diagnosis of detrusor sphincter dyssynergia (Figure 51.10). It should be noted, however, that in the majority of children, surface pad electrodes give excellent information about a composite view of muscle activity.

In select circumstances, a urethral pressure profile is helpful. Saline is infused at a rate of 2 mL/min, while the catheter is slowly withdrawn at 2 mm/s. The urethral pressure profile measures the passive resistance of a particular point in the urethra. To obtain dynamic information of the outlet during voiding, we use micturition urethral pressure profilometry. This study is done in the midvoiding cycle to help eliminate the transient responses of the bladder neck and external sphincter during micturition. In some sophisticated laboratories, microtipped transducer catheters are used rather than saline infusion.

Videourodynamics

Videourodynamics is a technique that simultaneously combines the evaluation of the anatomy of the lower tract with recorded urodynamic studies (Figure 51.11). In our facility, computer-generated digital images are stored and urodynamic parameters are superimposed on the image. Hard copies of the storage and voiding phase are also obtained and result in a radiologic interpretation component. Regardless of the imaging technology, videourodynamics is especially useful in delineating the bladder outlet during storage and voiding and identifying the causes of incontinence. When assessing the incontinent patient without uninhibited contractions noted on the cystometrogram, the urologist may evaluate the position and function of the bladder neck and proximal urethra under fluoroscopy to determine whether the urethra's incompetence or mobility is the etiology of the wetting. Videofluoroscopy may also be used to evaluate bladder compliance in relation to vesicoureteral reflux (VUR); i.e., reflux may act as a "pop-off" valve for elevation in detrusor pressure, and knowledge of the time of reflux relative to bladder pressure can be important for proper management with clean intermittent catheterization and anticholinergics (Figures 51.12 and 51.13).

The first leak through the bladder neck is recorded. McGuire et al. used videourodynamics and the abdominal leak point pressure (ALPP), also called the stress leak point pressure, to correctly diagnose the incontinent older patient with detrusor instability or ineffective outlet, as well as the pediatric patient with complex causes of incontinence (Figure 51.14). Videourodynamics easily evaluates the neurologically normal child with pseudosphincter dyssynergia and helps in the diagnostic dilemma of the child with neurogenic disease and decreased compliance, detrusor sphincter dyssynergia, and areflexic emptying (Figure 51.15).[36]

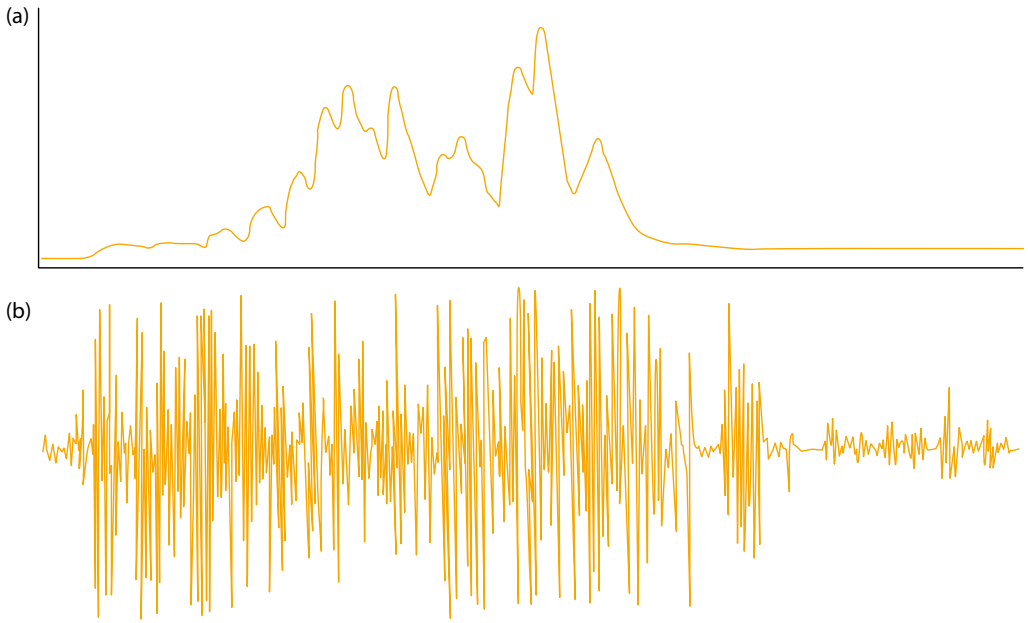

FIGURE 51.10 Urodynamics tracing in incontinent child with vesicosphincter dyssynergia: (a) uroflow; (b) electromyogram.

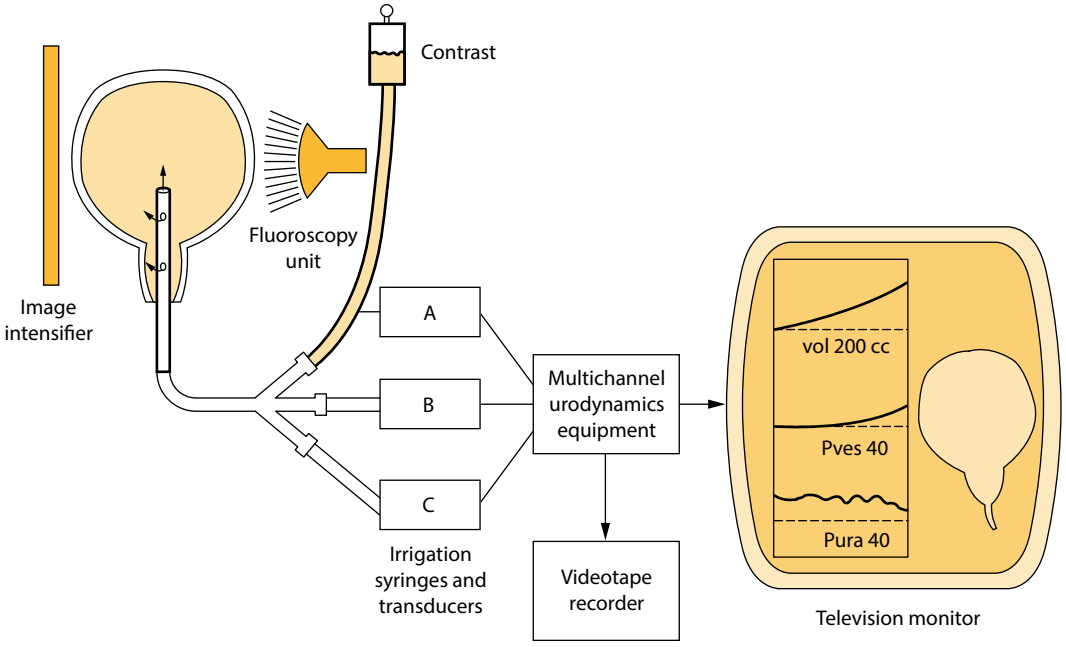

FIGURE 51.11 Videourodynamic equipment. (Modified from McGuire EJ, Cespedes RD, O'Connell HE. *Urol Clin N Am* 1996;23: 253–62. With permission.)

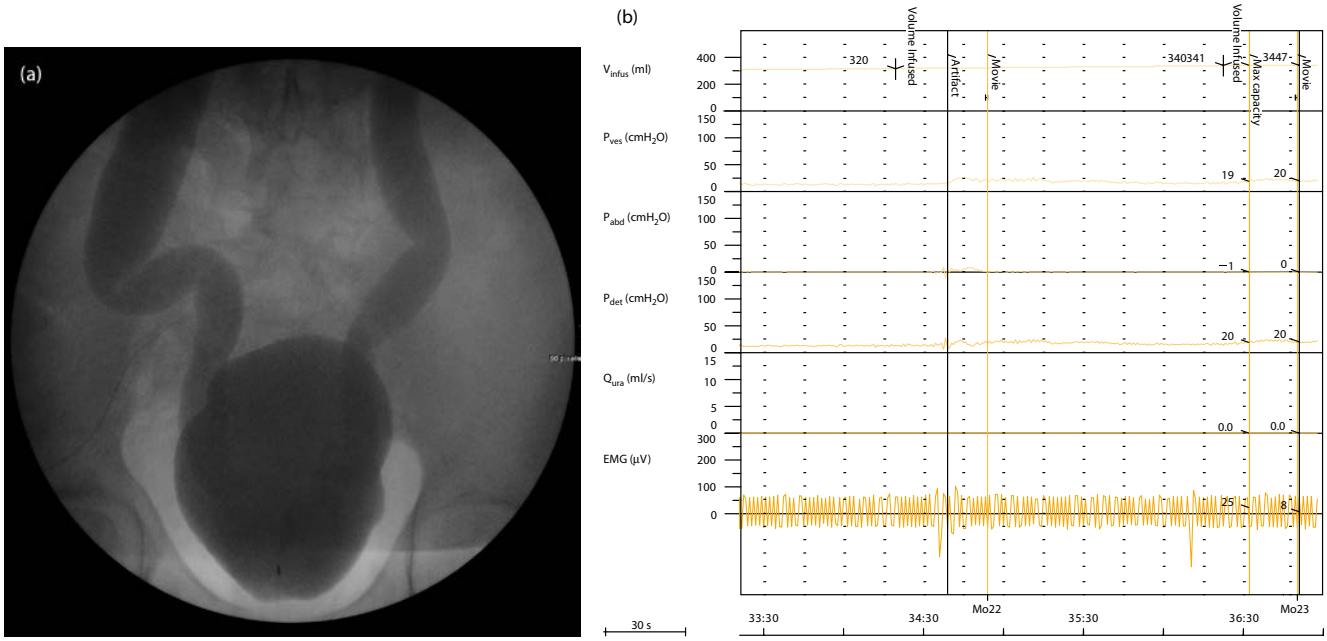

FIGURE 51.12 A 14-year-old male with imperforate anus, tethered spinal cord, and neurogenic bladder. He presents with recurrent urinary tract infection and incontinence despite clean intermittent catheterization and pharmacotherapy. (a) Videourodynamics were performed to evaluate the incidence of reflux and the bladder dynamics prior to further management. (b) Videourodynamics revealed a bladder capacity of 760 mL and low-pressure (19 cmH_2O) bilateral VUR. The bladder outlet was competent. Surgical options include augmentation cystoplasty with antireflux surgery. A Mitrofanoff and Malone antegrade colonic enema (MACE) procedure would be an option. V_{infus} = volume of infusete; P_{ves} = intravesical pressure; P_{abd} = abdominal pressure; P_{det} = detrusor pressure; Q_{ura} = urinary flow.

SUMMARY

Urodynamic evaluation is a powerful tool available to the pediatric urologist. Utilized in the proper setting, urodynamic studies can be helpful in both patients with NBD and patients with NNBD. It is our preference for children with NNBD to perform solely noninvasive urodynamic testing; however, in certain cases pressure studies are helpful in clarifying diagnosis and management. Children with neurogenic bladder undergo regular

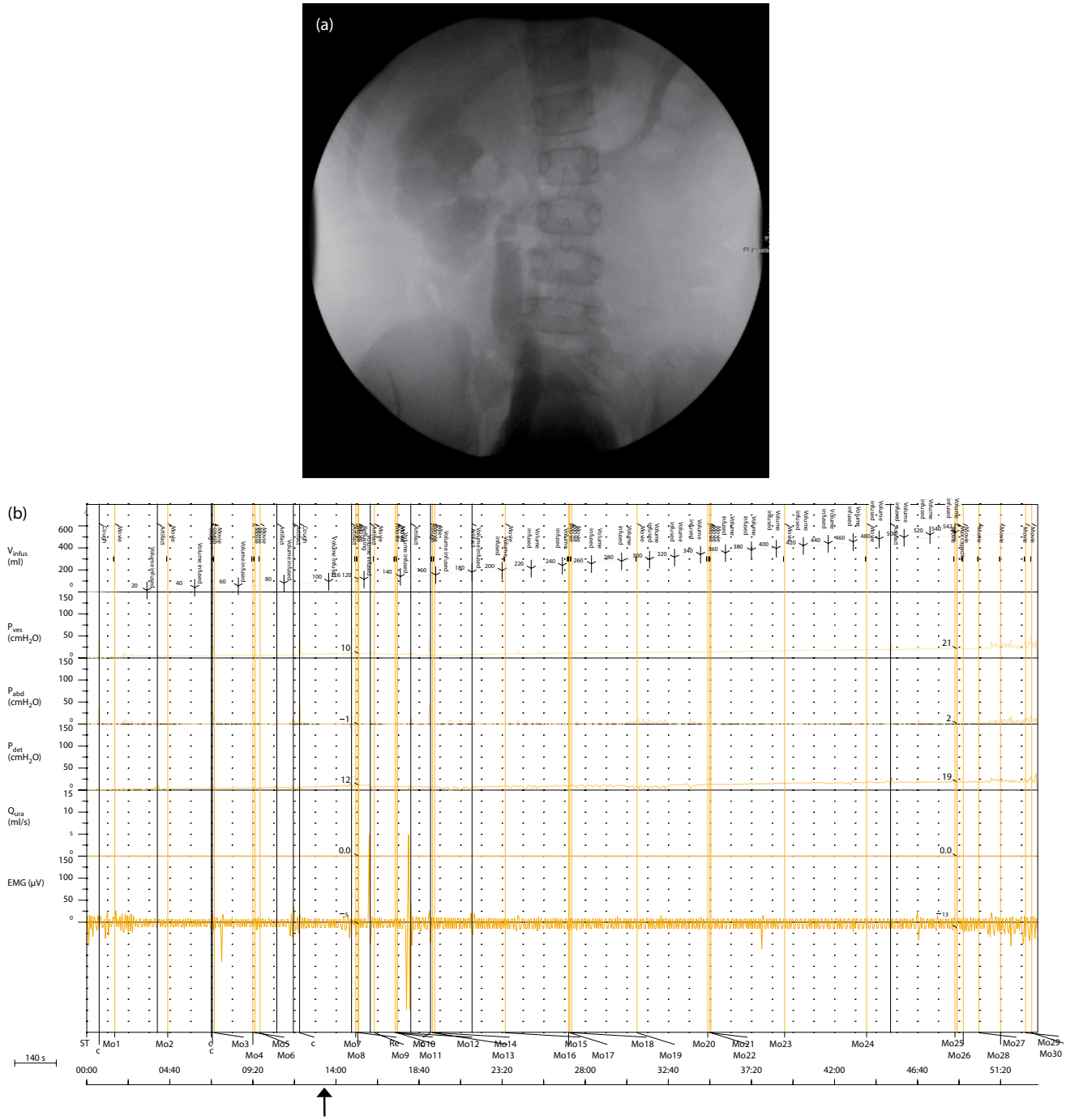

FIGURE 51.13 A 9-year-old female with dysfunctional elimination syndrome with recurrent febrile urinary tract infections. Videourodynamics revealed a bladder capacity of 875 mL, with no leakage. Her capacity pressure was 20 cmH_2O and she revealed grade 4 reflux at 117 mL (arrow) with a pressure of 10 cmH_2O. Her management included bowel management, biofeedback, and a subsequent successful subureteric injection of Deflux paste. V_{infus} = volume of infusete; P_{ves} = intravesical pressure; P_{abd} = abdominal pressure; P_{det} = detrusor pressure; Q_{ura} = urinary flow.

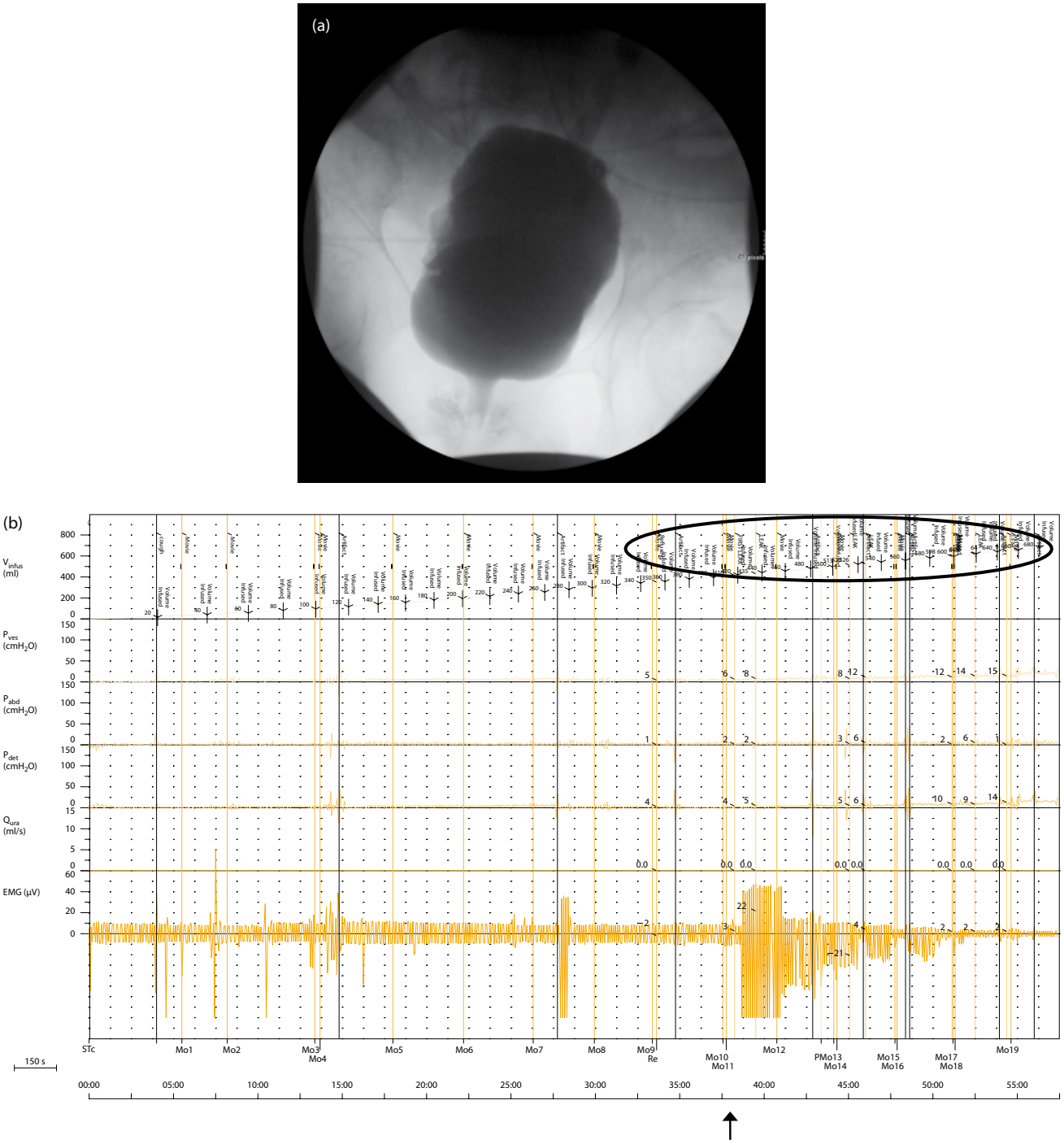

FIGURE 51.14 A 16-year-old male with L3–4 myelomeningocele had previous augmentation cystoplasty, Mitrofanoff and MACE procedure. He presented with continued incontinence, despite adequate anticholinergic therapy and clean intermittent catheterization (CIC) every 3–4 hours. His videourodynamic study revealed a bladder capacity of 810 mL. Radiographically, reflux occurred at 353 mL, (arrow) and the urethra was visible at his first leak point of 4 cmH_2O at 418 mL. His therapy included a sling procedure and a suburetric injection of Deflux paste. V_{infus} = volume of infusete; P_{ves} = intravesical pressure; P_{abd} = abdominal pressure; P_{det} = detrusor pressure; Q_{ura} = urinary flow.

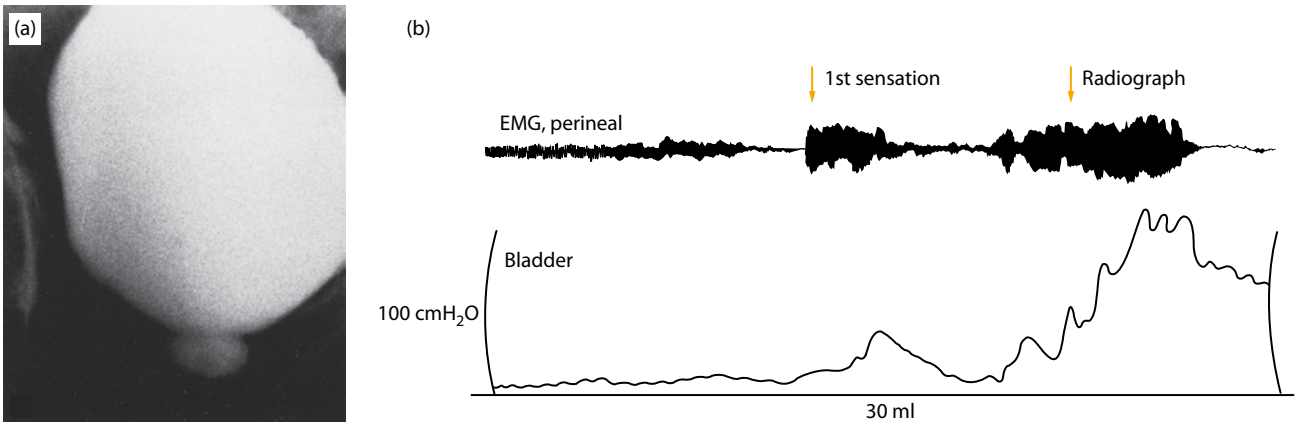

FIGURE 51.15 Videourodynamic study to indicate detrusor external sphincter dyssynergia. Note: detrusor contraction and simultaneous perineal EMG activity. The video indicates the dysfunctional void.

urodynamic studies to ensure proper management of bladder pressures to maintain continence and preserve renal function. Other children with progressive bladder disease, such as PUVs, also undergo regular urodynamic testing if clinical changes in bladder or renal function occur.

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CHAPTER 52

Neurological Control of Storage and Voiding

Julian Wan and Kate H. Kraft

INTRODUCTION

The storage and emptying of urine is controlled by a series of neurological pathways. These pathways are analogous to electrical circuits that help control the activities of a complex machine. They allow the lower urinary tract to shift rapidly between two different modes of function: storage and emptying. In infants, the transition between these two functions is subject to reflex control to produce involuntary voiding. In older children, urine storage and emptying are under voluntary control. This degree of control is unique in the body. Other visceral structures, such as the heart, bowels, and lungs, are controlled almost exclusively by autonomic or involuntary reflex mechanisms. They react to volitional activity but are not under a person's direct control. Yogis have been able to consciously slow their heart rate and rhythm, and elite athletes, such as Olympic target shooters, can delay the onset of their QRS complex, as seen on electrocardiogram (EKG), to allow them to fire between ventricular contractions. However, neither of these groups exhibit the degree of volitional control exerted over an autonomic system as experienced routinely by children over their bladder and urethra.[1–3] In more than a century of research, the physiology and neurology of the bladder and urethra have been fruitful areas of investigation, with better understanding acquired from clinical observation of patients, laboratory studies of human tissue, and animal models. For pediatric urologists, comprehension of the normal process of urine storage and drainage provides the foundation for our evaluation and treatment of congenital and acquired abnormalities of storage and emptying. This chapter reviews what is currently understood about these neurological pathways, their interaction with the target organs, and their clinical relevance to pediatric urology. Specific disease entities may be touched on by way of discussion, but these conditions (e.g., neurogenic bladder dysfunction) are discussed elsewhere in greater detail. The various components are first discussed, followed by the reflex pathways they help comprise. Finally, the role of higher centers and the plasticity of neurologic control are covered.

OVERVIEW SUMMARY

The lower urinary tract is composed of the bladder, urethra, and urinary sphincter. It has two principal functions: storage and emptying of urine. These actions are governed by a complex neural control system involving the brain, spinal cord, and autonomic and somatic nerves. This system performs as a series of circuits that overlay each other. At the most basic level, they serve as a simple switch to maintain a reciprocal relationship between the reservoir (bladder) and the outlet (urethra and urinary sphincter). They can also interconnect and create a complex sequence of coordinated selective excitation and inhibition of the bladder, urethra, and sphincter (Figure 52.1). A variety of neurotransmitters have been identified as playing significant roles in these pathways and may provide opportunities for pharmacological intervention. The urothelium also plays an important role in modulating bladder contractility. The lining of the bladder can be thought of as a sensory organ that tranduces physical and chemical signals to the afferent nerves and underlying smooth muscles.

During bladder filling, the viscoelastic properties of the bladder wall and an absence of an excitatory input from the parasympathetic ganglia to the bladder smooth wall musculature allow the bladder to accommodate more urine while keeping pressures low. This is unlike a balloon or other fixed container that cannot dynamically adjust and accommodate; its wall tension and storage pressure vary directly with infused volume. As the bladder continues to fill, an increase in outlet resistance occurs by means of a rhabdosphincter somatic reflex called the guarding reflex. In humans and many mammalian species, a sympathetic reflex also aids this process by increasing outlet resistance by increasing tension on the smooth muscle component of the sphincter and by inhibiting bladder contractility through an inhibitory effect on the parasympathetic ganglia. Finally, the sympathetic output also decreases the tension of bladder smooth muscle. Continence is maintained during increases in intra-abdominal pressure by the intrinsic competence of the bladder outlet with some reflex help from the rhabdosphincter.

Bladder emptying can be volitional or involuntary and involves an inhibition of the spinal somatic and sympathetic reflexes and activation of the parasympathetic pathways leading to the bladder. The coordinating center lies in the pons region of the brainstem and is otherwise known as the pontine micturition center (PMC). Initially, there is relaxation of the bladder neck and sphincter muscle, which is controlled by the cessation of somatic and sympathetic spinal reflexes, as well as local factors, such as nitric oxide (NO) that is released by parasympathetic stimulation.

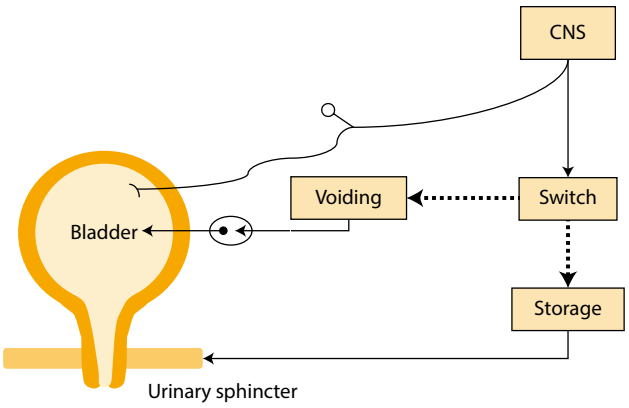

FIGURE 52.1 Schematic diagram illustrating the relationship between the anatomy of the lower urinary tract and the switch function of the micturition pathways. During urine storage, a low level of afferent activity activates efferent input to the urethral sphincter. A high level of afferent activity caused by bladder filling activates the switch in the CNS. This causes inhibition of the efferent pathway to the urinary sphincter, leading to relaxation, and excitation of the efferent pathway to the bladder, causing contraction and emptying.

After this has occurred, a coordinated, synchronized contraction of the bladder smooth muscle occurs. The bladder neck or outlet develops a funnel shape, which is due in part to the continuity of the bladder base and proximal urethra. There is modulation of this process from other peripheral reflexes and from supraspinal sources. The bladder then empties and normally drains to completion.

The ability to control and modulate between these two states develops with maturation. In neonates, the switch between the two modes of storage and emptying occurs reflexively once a threshold volume is reached. With maturation, the ability to modulate this action volitionally develops. This change occurs not because this early primitive set of pathways has been replaced by another. Instead, a layer of modulating and inhibitory controls that originate above the sacral spine are overlaid and mediated from the cerebral cortex and other higher centers. Once established, these pathways are not fixed but remain malleable throughout life. Injury and disease can cause these suprasacral inhibitory and modulating pathways to become lost or diminished. Earlier reflex pathways are then unmasked and can reemerge. Plasticity and resurfacing of earlier, more primitive pathways may help to explain the nature of many conditions due to neurogenic dysfunction. Even in adulthood, it appears that a significant degree of plasticity may be possible. This phenomenon offers potential in rehabilitating severe neurologic injuries and damage and may be of great research and practical importance in the near future.

TARGET ORGANS: BLADDER, URETHRA, AND URINARY SPHINCTER

The bladder and urethra are wrapped in a multilayer weave of smooth muscle. They are one anatomic unit but have two distinct functional regions: the body (or fundus) and the base and proximal urethra. The demarcation between these two areas roughly coincides with the division between the bladder body and the trigone.[4–6] They receive different types of autonomic innervation. Muscarinic cholinergic receptors are found throughout the smooth muscle but are most numerous in the fundus. Preganglionic cholinergic receptors in the sympathetic and parasympathetic ganglia are nicotinic, as are the cholinergic receptors of the striated muscle component of the urinary rhabdosphincter. Alpha-adrenergic receptors are more numerous in the smooth muscle of the posterior urethra and bladder base.[4–8] This cluster of alpha-adrenergic receptors is more concentrated in boys than in girls and is believed to explain the tight bladder neck closure seen during ejaculation.[9] Beta-adrenergic receptors are found in the fundus and act to help relax the bladder during filling.[10] Human fetal studies have shown that beta-adrenergic and cholinergic receptors are present as early as 3 months' gestation.[11] Alpha-adrenergic receptors appear in the trigone and urethra after 6 months' gestation.[6] These observations suggest that even very early in infancy, a complex system is already at work. The differences in receptor distribution have been exploited pharmacologically to create more precise acting drugs. This distribution is not static and can change due to injury or disease.

The organization of the bladder smooth muscle affects its normal function. Smooth muscles are organized into fascicles of 4–12 cells. Each fascicle is enveloped by extracellular matrix (ECM) consisting of collagen, elastin, and rare fibroblasts.[12] These bundles are arranged into circumferential and longitudinal patterns around the bladder and proximal urethra. The bundles are interwoven with no distinct layers. In males, the smooth muscle forms part of the prostatic capsule. The rhabdosphincter consists of circumferential fibers of striated muscle that surround the smooth muscle from the bladder base to the urogenital diaphragm.[13] It appears that the rhabdosphincter is distinct and separate from the urogenital diaphragm and pelvic-supporting striated muscles in both males and females.[14,15] The striated muscles are both fast and slow twitch. The fast-twitch, more easily fatigued fibers are used during voluntary attempts to stop micturition or during acts of active suppression of voiding, such as Vincent's curtsy. The slow-twitch, fatigue-resistant fibers contract during bladder filling as part of the guarding reflex. The rhabdosphincter initially behaves in a reflex fashion but later comes under volitional control from the higher cortical centers with maturation. In addition to somatic and sensory connections, the urinary sphincter also receives parasympathetic and sympathetic fibers from the pelvic plexus, making it "triple innervated."[16] Clinically, this concept is important, as alpha-blockers have been shown to be useful in treating urinary obstruction and dysfunctional voiding. This combination of sympathetic, parasympathetic, and somatic innervation has been clearly demonstrated in the cat and has been corroborated in humans with regard to the adrenergic sympathetic component. The full functional significance of the autonomic innervation of the striated sphincter in humans is not yet defined. Autonomic dysfunction of the sphincter has been found in patients with lower motor neuron lesions but is not seen in patients with functional issues, such as detrusor sphincter dyssynergia (DSD), suggesting that the degree of autonomic

innervation can change as a response to injury or disease in a manner not seen in normal individuals.[4,17]

Nerve endings do not innervate each individual smooth muscle cell of the human bladder. Electron microscopy shows that normal muscle cells are about 0.2 nm apart without intercellular links.[4] Direct cell-to-cell excitation has not been shown. Efficient coordinated detrusor contractions are propagated by electromechanical coupling and not by direct neuronal excitation. A few muscle cells are directly triggered, which in turn contract and pull on their neighboring cells, thereby triggering further excitation. Myogenic changes may be responsible for urge and urge incontinence seen with overactive bladder.[18,19] These changes could occur directly or as a reaction to stimuli or alterations to the overlying urothelium.

The normal bladder exhibits excellent compliance and viscoelasticity. These properties are influenced by the properties of the ECM, which is a mixture of collagen, elastin, and occasional fibroblasts. In many pathological states, there are changes in the ECM that affect the mechanical function of the bladder. The type of collagen that is laid down appears to play an important role.[20] Types I and III predominate in the ECM. Type I is thicker and stiffer. Type III is thinner and more pliable. As the human fetus ages, the ratio between types I and III decreases with an associated rise in bladder compliance and increase in elastin. A normal fetal bladder becomes more compliant as gestation progresses. Fibroblasts in the interstitium are the source of most of the connective tissue, and normally in the bladder there is little fibroblast activity. Denervation experiments show that increases in ECM may be in part due to a slowing of collagen degradation and decrease of activity of local proteases. Increases in ECM come not only from the fibroblasts but also from the smooth muscles themselves.[21] Dedifferentiation of smooth muscle cells under repetitive stress leads to more elaboration of collagen and elastin in the interstitium. This resembles the process seen in stressed walls of vasculature, wherein an injury or disease can initiate a spiraling cascade of pathology. A neurogenic bladder, for example, may lose the neurologic modulation that maintains compliance, which in turn leads to higher storage pressure that causes higher stress, which then promotes dedifferentiation of smooth muscles and greater deposits of elastin and collagen. This creates a vicious cycle of deteriorating elasticity and compliance. Removal or alteration of normal innervation may therefore result in lasting changes to the histology of the bladder.

NEUROTRANSMITTERS AND THE UROTHELIUM

The basic autonomic neurotransmitters are well known. The sympathetic nerves are adrenergic and use norepinephrine as a neurotransmitter in postganglionic synapses. Preganglionic sympathetic and all parasympathetic nerves are cholinergic and use acetylcholine (ACh). Less well known is a third system, the purinergic or peptidonergic system. Found in animals and humans, it comprises a wide variety of molecules, including vasoactive intestinal peptide (VIP), neuropeptide Y, adenosine triphosphate (ATP), substance P, somatostatin, and calcitonin gene-related peptide (CGRP).[4,22,23] This third pathway is believed to act as a modulator of overall autonomic activity. Neuropeptides have been found throughout the smooth and striated muscle of the lower urinary tract. In addition, from observations in some pathological states of autonomic denervation, the effects of these neurotransmitters are thought to be clinically more significant. The existence of this third pathway of the autonomic system was inferred when muscarinic blockade with atropine did not completely ablate in vitro bladder muscle contraction.[7] Atropine also seemed to be less effective in blocking bladder muscle contractions from specimens taken from neurogenic bladders, suggesting that there was an enhanced purinergic factor in these pathologic bladders.

Complicating the discussion is the role that the urothelium may play in how these neurotransmitters are released and modulated. The urothelium is not just a barrier between the urine and the underlying tissues of the bladder. It also acts as a sensory organ by transducing physical and chemical signals to the attendant afferent nervous system and underlying smooth musculature (Figure 52.2). The urothelium influences the detrusor smooth muscle by modifying its contractility and the extent of spontaneous activity. The urothelium responds to different forms of stress and stimuli. Urothelial cells have receptors that respond to mechanical changes: norepinephrine, ACh, purines, and many transient receptor potential vanilloid channels (TRPV). Stimulation of any of these urothelial sensory structures can lead to the release of active agents, such as ATP, ACh, and NO, which have both excitatory and inhibitory effects on the afferent nerves located in or near the urothelium. For example, mechanical stress results from changes in transmural bladder pressure, storage pressure, and increased lateral tension. These mechanical stresses become transduced to afferent signals using several different pathways that may play a pathological role in both overactive and underactive bladder syndromes.[24–28] Several purinergic transmitters are inhibitory: opioid peptides (enkephalins), inhibitory amino acids (glycine and gamma-aminobutyric acid [GABA]), serotonin, dopamine, and nonopioid peptides, such as neuropeptide Y and corticotrophin-releasing factor. All these can inhibit the micturition reflex when applied to the central nervous system (CNS). Excitatory purinergic transmitters include glutamic acid, neuropeptides such as substance P and VIP, NO, and norepinephrine.[29,30] These neurotransmitters also affect the vascular smooth muscle, may alter local blood flow, and can appear in increased concentration in obstructed or neurogenic bladders. VIP has been found to be lower in concentration in biopsy specimens of hypercontractile bladders.[31] A compensatory role for VIP and neuropeptide Y in the urethras of patients with spinal cord injury has been suspected because of their elevated levels.[32] ATP plays a well-known and important role as the basic molecule for energy transfer in the human body. Abundant in the cytoplasm, ATP is released into the extracellular space by several mechanisms: vesicular exocytosis or by selective channels. The level of ATP rises in response to distention and acts on P2X2 and P2X3 receptors on the afferent neural plexus.[33–35]

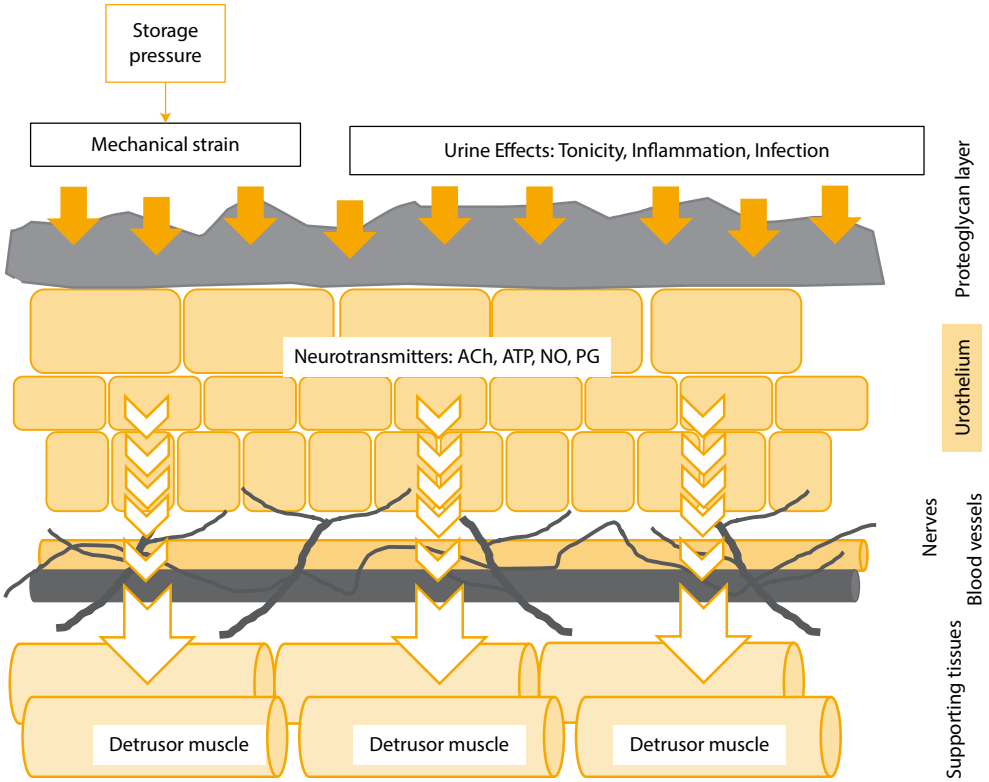

FIGURE 52.2 Schematic diagram illustrating the role of the urothelium in transducing and modulating the effects of neurotransmitters.

ATP levels have been found to be higher than normal in the bladder muscle of spina bifida patients and interact with two families of receptors, P2X and the G protein coupled on P2Y.[6] Therefore, it has been speculated that hyperactivity observed in neurogenic and obstructed bladders may be the result of abnormal purinergic influences mediated by these neurotransmitters.[36]

Cholinergic receptors are found throughout the smooth muscle of the lower urinary tract and are numerous in the body of the bladder but have subtle variations.[8] At least five subtypes of muscarinic receptors exist (M1–M5). Types M1, M2, and M3 are found in the human bladder.[37] Types M2 and M3 may act synergistically, with M2 enhancing the effect of M3-mediated contractions. Stretch and strain have also been shown to induce ATP release by alpha-adrenergic 1 receptors (using NE), TRPV1 agonists, and antimuscarinic agents via M2/M3 receptors. The M2 type may also modulate smooth muscle relaxation. Types M2 and M4 together may play a role in the prejunctional inhibition of ACh release.[38] The identification of subtypes makes possible the development of receptor-specific agents, which act not just to crudely block the postjunctional receptor but also to possibly modulate prejunctional release. The preganglionic cholinergic receptors in the sympathetic and parasympathetic ganglia in contrast are nicotinic, as are the cholinergic receptors in the rhabdosphincter. Pancuronium, an anesthetic, and botulinum toxin, both nicotinic-blocking agents, may be used to paralyze the rhabdosphincter, but total incontinence does not result because the smooth muscle component of the sphincter and bladder neck remains unaffected.[39]

Botulinum neurotoxin type A (Botox A), along with beta-3 adrenergic receptor agonists and phosphodiesterase type 5 (PDE-5) inhibitors, offers new ways of interacting with the cholinergic system. It may be an alternative to the classic antimuscarinic agents in the treatment of conditions such as overactive bladder.

At the neuromuscular junction, Botox A inhibits release of ACh from efferent cholinergic nerves at the neuroeffector junction and ganglion. In the epithelium, it may inhibit stretch-induced ATP release, as seen in spinal cord injury and cystitis patients.[40–42] Recent findings suggest that botulinum toxin A, beta-3 adrenergic receptor agonists, and PDE-5 inhibitors at lower concentrations can directly inhibit afferent excitation without decreasing detrusor contractility. The clinical impact is that these drugs alone or in combination may help treat the sensory component of lower urinary tract dysfunction without affecting contractility. Normally, Botox A inhibits the parasympathetic nerves, but in some pathologic disease states, it may be preferentially taken up by the afferents because of their increased activity. Beta-3 adrenergic agonists can indirectly decrease afferent excitability by inhibiting intrinsic activity through smooth muscle relaxation without affecting contractility. PDE-5 inhibitors appear to have little effect on contractility because guanylyl cyclase concentrations are very low in detrusor smooth muscle. Beta-3 agonist receptors are stimulated by endogenous NE released during the filling phase to promote bladder relaxation and facilitate bladder storage (Figure 52.3).

As noted earlier, alpha-adrenergic receptors are concentrated in the trigone, bladder neck, and posterior urethra

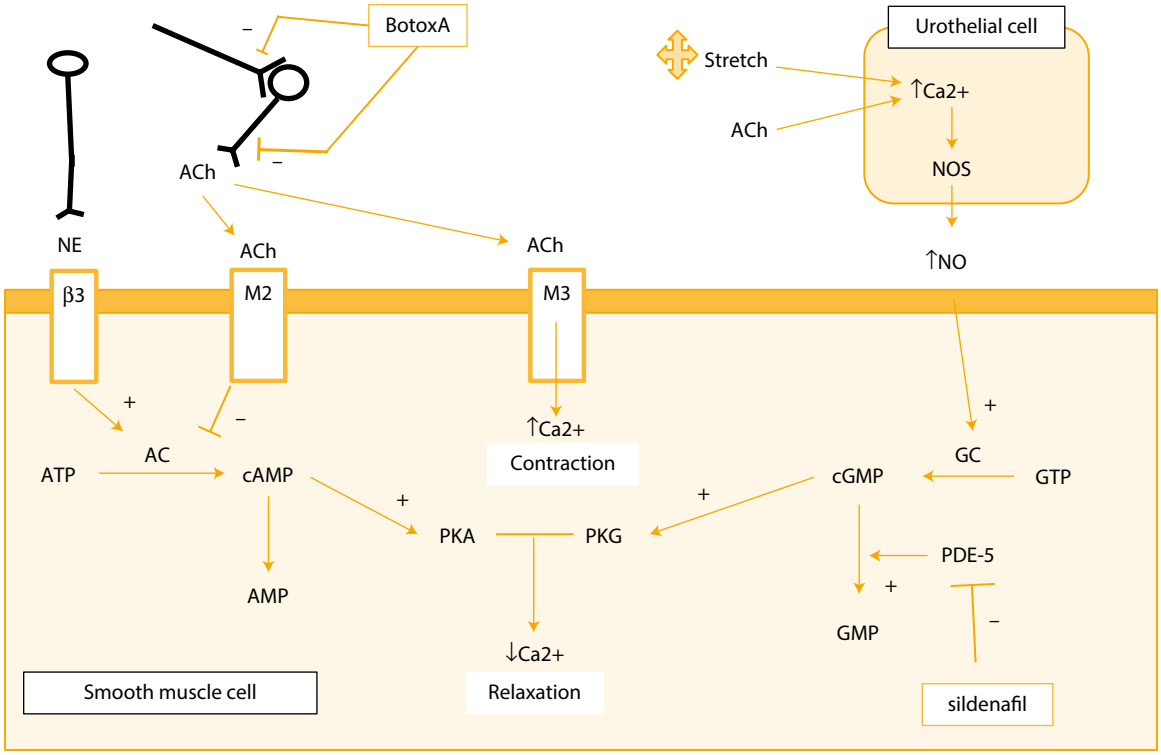

FIGURE 52.3 Schematic diagram showing the relationship between the different receptors (β3, M2, M3) and the effect of agents such as Botox A and sildenafil. Ca^{2+} = calcium, NOS = nitric oxide synthase, AC = adenylyl cyclase, PKA = protein kinase A, PKG = protein kinase G, GC = guanylyl cyclase, cAMP = cyclic adenosine monophosphate, cGMP = cyclic guanosine monophosphate.

and are more numerous in boys than girls.[8] Stimulation of beta-adrenergic receptors in the detrusor leads to relaxation of the smooth muscle. The effect is mediated via adenylyl cyclase, which leads to accumulation of cyclic adenosine monophosphate (cAMP). This observation led to speculation that beta-blockers could be used directly or that PDE inhibitors, which slow the breakdown of cAMP, could be adapted as drugs for treating bladder instability.[43] Hypogastric nerve stimulation and alpha-adrenergic agonists produce a rise in intraurethral pressure that is blocked by alpha-antagonists.[44] This supports the role for alpha-agonist agents in treating some forms of incontinence and alpha-blockers in relaxing the bladder neck and urethra. NO has been identified as a major inhibitory transmitter mediating relaxation of the urethral smooth muscle during micturition.[45] Parasympathetic postganglionic nerves release NO. Relaxation is blocked by inhibitors of NO synthase. NO is also involved with bladder afferent modulation. In situations of bladder irritation, NOS inhibitors can help decrease or eliminate bladder instability. NO-mediated smooth muscle relaxation is due to increased intracellular accumulation of cyclic guanosine monophosphate (cGMP). Like cAMP, it is inactivated by PDE and may be a target for PDE inhibitor drugs. Originally developed to treat hypertension and later erectile dysfunction, PDE-5 inhibitors have been shown recently to have a beneficial effect on lower urinary tract dysfunction.[46–49] The sites of action in the bladder remain unclear. PDE enzymes break down cyclic nucleotides, and PDE-5 inhibitors prevent the breakdown of cGMP, which increases the activity of protein kinase G (PKG), which in turn may inhibit contractility. Current studies of selective inhibitors of PDE-5 have shown their beneficial effects for lower urinary tract symptoms, including bladder overactivity.[47,50] Neuropeptides, such as substance P, neurokinin A, CGRP, VIP, pituitary adenylate cyclase-activating peptide (PACAP), and enkephalins, play a role in modulating afferent sensory nerves. The actions of these purinergic transmitters have led to the recognition that the bladder urothelium can be viewed in totality as a large sensory organ, and to the regarding of the urothelium as an integral part of the afferent pathway in much the same way that the detrusor and rhabdosphincter are considered distinct components.[51,52] Their actions help shape and form the type of afferent signal that enters the micturition reflex. This concept has led to novel approaches in treating conditions such as overactive bladder and interstitial cystitis. Rather than focusing on the efferent pathways, new treatments and therapies aim to dampen or alter the afferent signals from the urothelium.[51–53] For example, neuropeptides have been found to be active in capsaicin-sensitive C-fiber bladder afferents. These afferents are of particular interest because they seem to be normally quiescent but become very sensitive when faced with major bladder inflammation or other noxious intravesical events.[54–56] They can be desensitized by agents directed against vanilloid receptors. Capsaicin and its analogue resiniferatoxin have attracted recent interest because of their potent ability to affect the vanilloid receptors and desensitize these C-fibers.[57]

An intact urothelium is associated with increased spontaneous contractile activity in the bladder. It causes

high-frequency, low-amplitude contractions to convert into larger, more prolonged, and less frequent contractions. Two proposed theories have developed from observations seen in whole bladder preparation in vitro. First, the epithelium itself may be triggering the spontaneous contractions. Second, the epithelium through either cell-to-cell interaction or release of some diffusible agents is affecting detrusor function. Practically, this may explain why overactivity is often seen symptomatically when any inflammatory or infectious process results in denuding of the urothelium; it may be a fundamental effect related to changes in the urothelium and not wholly due to the inflammation alone.

As noted above, the urothelium releases substances that have an inhibitory or dampening effect on smooth muscle contractility, including NO, prostaglandins, and adenine nucleotides. However, there is no clear understanding of the role that these substances play in the normal physiological or pathophysiological control of bladder contractility. The bladder epithelium is theorized to metabolize or otherwise inactivate the excitatory agonist, to act as a barrier to the diffusion and penetration of these agonists to the detrusor muscle, or to respond to the agonists by releasing substances that reduce the contraction of the underlying muscle. Experimental bladder preparations have suggested these possible mechanisms, but to date the exact inhibitory pathway is not known to be mediated by any of these pathways.[55–57]

Treatments that affect the urothelium can lead to either dysfunction or benefit. Removal of the damaged or diseased urothelium (such as the use of laser therapy for forms of ulcerative interstitial cystitis) may help decrease bladder and pelvic pain. The formation of fresh urothelium after treatment has been associated with symptom-free periods of as long as 6–12 months. The turnover time of urothelial cells is about 200 days, which may explain the mechanism of relief. It remains unclear how much, if any, benefit can be associated with the barrier function of the urothelium. The surface proteoglycans and tight junctions of the urothelial membrane and uroplakins may play a key role.[56–57]

Intravesical administration of drugs may allow maximal dosing while minimizing associated side effects. There is a long history of using intravesical oxybutynin in the treatment of neurogenic bladder.[58,59] The low permeability of the urothelium, the dilution of the drug, and the later washout remain limiting factors. Permeability enhancement agents that improve transport across the bladder urothelial wall or mucoadhesive drug delivery systems that strongly adhere to the urothelium and ensure drug persistence near the site of action may be potential therapeutic mechanisms. Strategies that have been investigated include polymeric hydrogels and the use of electromotive force, drugs that temporarily disrupt the urothelial integrity, and nanocarriers such as liposomes. Electromotive drug administration uses electric field stimulation to enhance the transport of hydrophilic drugs. Agents that have been administered in this manner include protamine sulfate, which temporarily disrupts urothelial integrity, and dimethyl sulfoxide, which can penetrate without leaving significant damage.[60–62]

PERIPHERAL INNERVATION

The peripheral innervation of the lower urinary tract includes components of the sympathetic, parasympathetic, and somatic nervous systems. They connect to the target organs of the bladder, urethra, and urinary sphincter by the pelvic, hypogastric, and pudendal nerves. There are also modulating influences from the sympathetic ganglia chain and intramural ganglia.

The pelvic nerves are parasympathetic and originate from the sacral spinal cord. They excite the bladder and relax the urethra and urinary sphincter. The efferent nerves originate from the upper and middle sacral spinal cord segments S2 to S4 and course outward as the pelvic nerves. Parasympathetic preganglionic neurons (PGNs) are located in the lateral part of the sacral intermediate gray matter in the region termed the sacral parasympathetic nucleus (SPN), and the axons exit the ventral roots to reach the peripheral ganglia. In humans, parasympathetic postganglionic neurons are located in the detrusor wall layer, as well as in the pelvic plexus. Patients with cauda equina or pelvic plexus injury may be neurologically decentralized but are not completely denervated. Afferent and efferent neuron interconnections at the level of the intramural ganglia are still possible.[55]

The hypogastric nerves are sympathetic and arise from the lumbar spinal cord. They excite the bladder base, urethra, and urinary sphincter. The efferent sympathetic nerves originate from spinal cord segments T11 to L2. These nerves pass from the cord to the lumbar chain ganglia and then to the superior hypogastric plexus. Nerves from the plexus coalesce to form the right and left hypogastric nerves. Sympathetic pathways arise from the rostral lumbar spinal cord and provide noradrenergic excitatory and inhibitory activity to the bladder and urethra.[53] Activation of the sympathetic nerves causes relaxation of the bladder body and contraction of the bladder outlet and urethra, which facilitates storage of urine.

The pelvic and hypogastric nerves meet to form the inferior hypogastric plexus. Nerves from this plexus then travel to the lower ureter, bladder, urethra, and urinary sphincter. The preganglionic nerves of the hypogastric plexi are closely associated with the ganglia close to or within these target organs. Intramural ganglia have been identified in the adventitia, muscle, and suburothelium of the bladder and urethra. Postganglionic nerves from the intramural ganglion then travel the final distance to directly innervate the smooth muscle lining these organs. This last group of ganglia and nerves comprises the so-called "urogenital short-neuron system."[5,39]

The pudendal nerves excite the rhabdosphincter. They are somatic and arise from the sacral cord segments S1 to S4. The nucleus of these nerves resides in the lateral border of the ventral horn of the sacral cord, called Onuf's nucleus after Wladislaus Onufrowicz, Swiss anatomist, 1836–1900. Found in cats, dogs, and humans, it also innervates the bulbocavernosus and ischiocavernosus muscles. The rhabdosphincter initially behaves reflexively and later comes under voluntary control from the higher cortical centers with maturation. The sphincter motor neurons have dendrites that project laterally to the lateral

funiculus, dorsally to the intermediate gray matter, and dorsomedially to the central canal. These connections with interneurons allow for a complex pattern of reflexes to be created. In addition to somatic and sensory connections, the urinary sphincter also receives parasympathetic and sympathetic fibers from the pelvic plexus, making it "triple innervated." This combination of sympathetic, parasympathetic, and somatic innervation is modeled well in the cat and has been corroborated in humans, particularly the adrenergic sympathetic component.[16]

The ability to sense fullness is important to both the storage and emptying of urine. Afferent activity that occurs during bladder contraction has an important reflex function and appears to reinforce the central drive that maintains the detrusor contractions. All these named nerves also carry afferent sensory information back to the spinal cord.[55] Afferent nerves travel along the hypogastric and pelvic nerves to link the urogenital smooth muscle to the hypogastric plexus and further upward to the lumbar and sacral dorsal root ganglia. Afferent sensory nerves also travel along the pudendal nerve to the sacral spinal cord. These nerves conduct information from the bladder suburothelium and muscle, including the sense of fullness, urgency, and pain. The primary afferent nuclei of the pelvic and pudendal nerves are contained in the sacral dorsal ganglion (DRG), while the afferent innervation of the hypogastric nerves comes from the rostral lumbar DRG. The central axons of these DRG neurons carry the sensory information to the second-order neurons within the spinal cord.[55,63] Visceral afferent fibers of the pelvic nerve and pudendal nerve enter the cord and move within the portion of the dorsal cord called Lissauer's tract, named for Heinrich Lissauer, German neurologist, 1861–1891.[63,64] This is a longitudinal bundle of thin, unmyelinated, and poorly myelinated fibers capping the apex of the posterior horn of the spinal gray matter, composed of posterior root fibers and short association fibers that interconnect neighboring segments of the posterior horn. Pelvic nerve afferents monitoring bladder volume and degree of contraction are carried on both myelinated and unmyelinated axons. The myelinated axons are alpha-delta fibers, and the unmyelinated are C-fibers. Neuropathic conditions and possibly inflammatory conditions can lead to recruitment of C-fibers, which can form new functional afferent pathways that are believed to cause urge incontinence and possibly increased bladder pain. Alpha-delta fibers carry information from smooth muscle and sense wall tension. When inflamed, there is increased discharge at a lower threshold pressure. The C-fibers carry stretch and bladder fullness sensation from the urothelium and smooth muscle and act as nociceptors for overdistention. Usually quiet when irritated, they can discharge at lower threshold and unmask a new afferent pathway during inflammation. This has formed the basis for several lines of treatment that act against the sensory end (e.g., capsaicin and resiniferatoxin). Current theory holds that several different types of afferents are present: stretch, volume, tension, and silent (nociceptors). Irritation intravesically can lower the pressure threshold. Most C-fibers are insensitive to normal distention but can become mechanosensitive and active when irritated or inflamed. As noted earlier, afferent signaling is subject to multiple layers of modulation and a variety of stimulatory and inhibitory agents.

REFLEX PATHWAYS

Several reflex pathways help mediate urinary storage and emptying. The standard model describes the central pathways that control the lower urinary tract function as being organized as simple on–off switching circuits. Some reflexes promote urine storage and others facilitate voiding. These reflexes do not act in isolation but are interlinked to create complex feedback mechanisms. The guarding reflex that links bladder distention to external sphincter activity during filling can activate, in turn, sphincter afferents that inhibit the parasympathetic excitatory inputs to the bladder. This explains how bladder-to-rhabdosphincter activity could lead to decreased bladder activity during storage. The disruption or discoordination of these interactions may be the underlying cause in forms of neurogenic bladder dysfunction (Figures 52.4 and 52.5).

There are four types of pathways in the spinal cord that link together to form the reflex pathways: (1) spinal efferent nerves, which include autonomic PGNs and somatic motor neurons; (2) spinal interneurons, which are located between the dorsal and ventral horns; (3) primary afferent neurons; and (4) central neurons from the brain and brainstem that modulate spinal reflexes.[56] These pathways were elucidated using intracellular labeling, pseudorabies virus tracing, and measurement of gene product expression.[65]

Urine Storage, Guarding, and Sphincter-to-Bladder Reflex

During the storage of urine, distention of the bladder causes afferent nerves to be stimulated. These in turn trigger sympathetic excitatory outflow to the bladder trigone and urethra and pudendal outflow to the rhabdosphincter. These responses together have been collectively labeled the guarding reflex. Sympathetic stimulation also inhibits detrusor muscle and bladder ganglia transmission. The guarding reflex in turn becomes inhibited during the start of micturition.[55,66] This sequence of reflex activity is demonstrable clinically. During bladder filling, there is an involuntary increase in the activity of the rhabdosphincter detected on urodynamics, which is measurable by either an intraluminal pressure transducer placed at the highest pressure zone of urethral pressure or by perineal electromyography (EMG) (Figure 52.6). During bladder filling, the EMG of the urinary sphincter will show increased activity, reflecting the increase in the efferent firing in the pudendal nerve and an increase in outlet resistance that contributes to the maintenance of continence. The intraluminal pressure will drift upward. This variation is not accidental or random and is related to bladder activity. The external urethral sphincter activity reaches a peak just before the onset of micturition. At low bladder volume, the reflex is involuntary, but as the volume continues and the sensory threshold of fullness of the bladder is reached, the external urethral sphincter activity increases and becomes

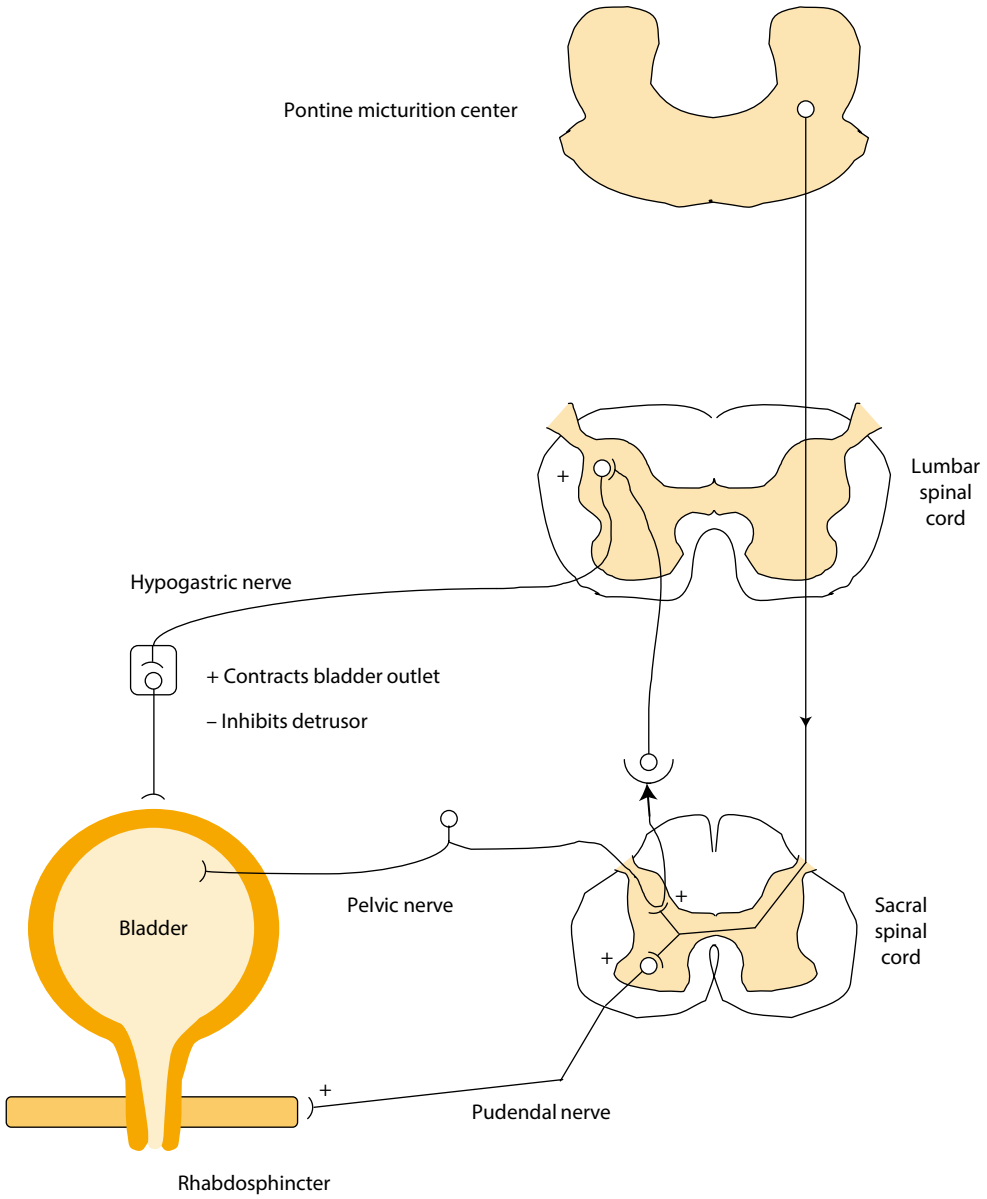

FIGURE 52.4 During storage, distention of the bladder causes low-level bladder afferent activity. This in turn activates the sympathetic outflow to the bladder and urethra and increases pudendal nerve activity to the rhabdosphincter. These constitute the guarding reflex. Sympathetic activity also inhibits detrusor activity and transmission in the bladder ganglia.

a conscious and voluntary phenomenon. While bladder afferent stimulation is the primary activation of pudendal motor neuron activity, urethral and perineal afferents may also contribute.[66,67] This part of the guarding reflex links proprioceptive afferents from the pelvic floor to induce closure of the urethral outlet.

It was originally theorized that this reflex increase may be a mechanism that protects against stress incontinence.[68] For clinicians, it is probably more relevant as a way of explaining signs and symptoms in patients who are infrequent voiders or who are trying to ward off urgency. This mechanism explains how certain avoidance maneuvers, such as vigorously crossing the legs repeatedly and "squirming" (doing the "potty dance") or tucking the heel into the perineum (Vincent's curtsy), are used by children who are infrequent voiders to dampen feelings of urgency, thereby allowing them to prolong holding of urine. This observation is further supported by data that stimulation of the somatic afferent pathways of the pudendal nerve to the caudal lumbosacral spinal cord can inhibit voiding. Afferent input can come from a variety of sites, such as the penis, vagina, rectum, perineum, urethral sphincter, and anal sphincter. This aspect has been termed the sphincter-to-bladder reflex pathway. Studies in cats suggest that this is mediated by suppression of the interneuronal pathways in the sacral spinal cord and also by direct inhibition of the parasympathetic PGNs.[69] Sympathetic firing is initiated at least in part by a sacrolumbar intersegmental spinal reflex pathway that is triggered by vesical afferent activity in the pelvic nerves. The vesicosympathetic reflex represents a negative feedback mechanism whereby an increase in bladder pressure triggers an increase in inhibitory input to the

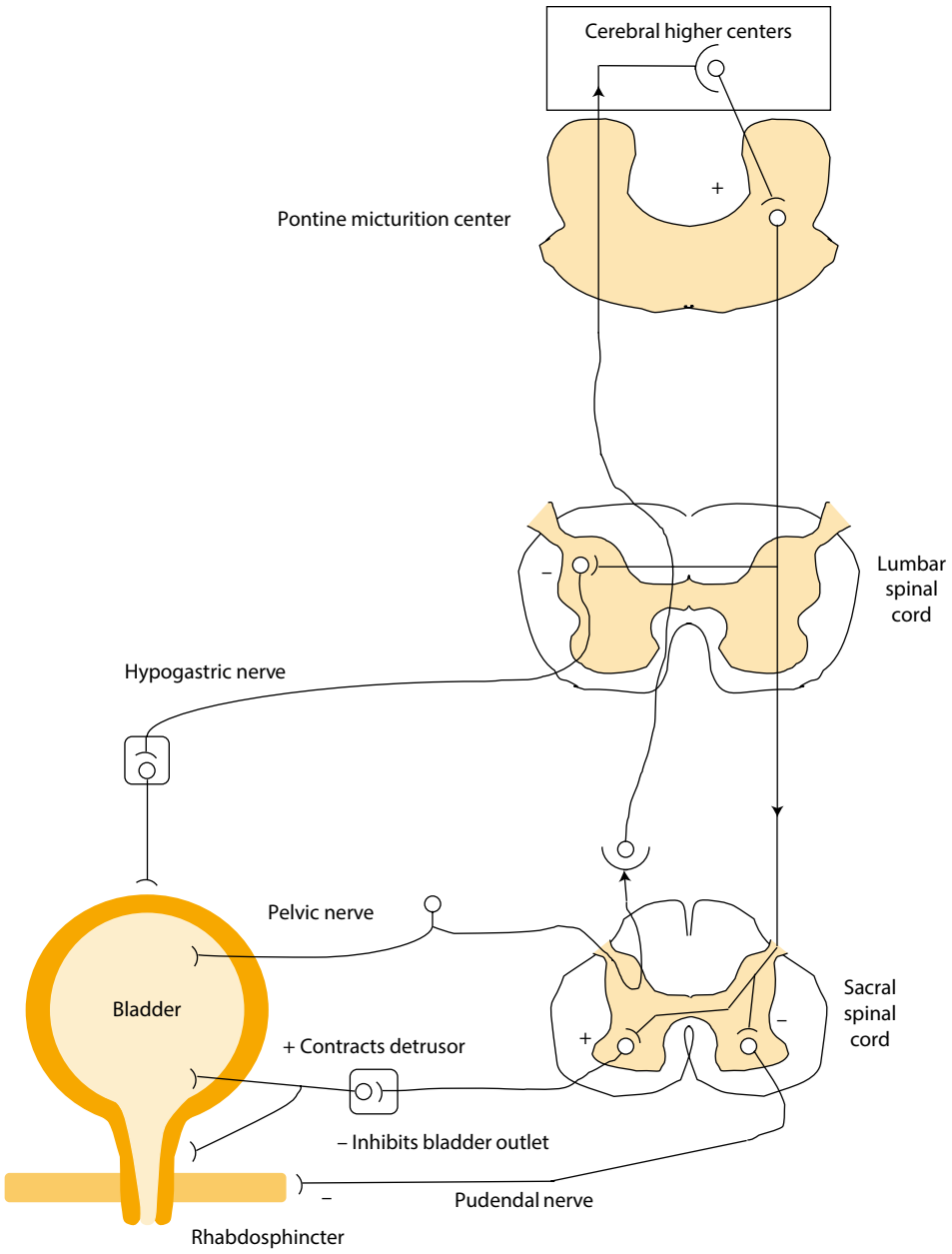

FIGURE 52.5 At the initiation of voiding, bladder afferent activity increases, which activates the PMC. This inhibits the spinal guarding reflexes, which are conducted via the pudendal nerve. It also stimulates the parasympathetic outflow to the bladder and bladder neck. Ascending afferents complete the reflex loop by bringing feedback input to the cerebral cortex and higher centers.

bladder, thus allowing the bladder to accommodate larger volumes of urine. The reflex pathway is inhibited during voiding, and this inhibition is in turn abolished by transection of the spinal cord at the thoracic level, suggesting that it originates at a supraspinal site, probably the PMC.

Voiding or Micturition Reflex

The switch from storage to the voiding phase can occur voluntarily or reflexively. Infants and patients with neuropathic bladder demonstrate the former when the volume of urine exceeds the threshold volume beyond which micturition occurs (Figures 52.5 and 52.6). At that point, increased afferent firing from the tension receptors in the bladder leads to a shift in the efferent activity. Sympathetic and somatic pathways are inhibited, and sacral parasympathetic activity increases. There is an initial relaxation of the urethral sphincter, followed a few seconds later by the contraction of the bladder, an increase in bladder pressure, and a flow of urine. Relaxation of the urethral smooth muscle during micturition is mediated by parasympathetic stimulation to the urethra that triggers the release of NO, which acts as an inhibitory transmitter, and by removal of excitatory inputs to the urethra. The parasympathetic outflow to the detrusor and urethra has a more complicated central organization involving spinal and spinobulbospinal pathways passing through the PMC. When this coordination is disrupted as a result of

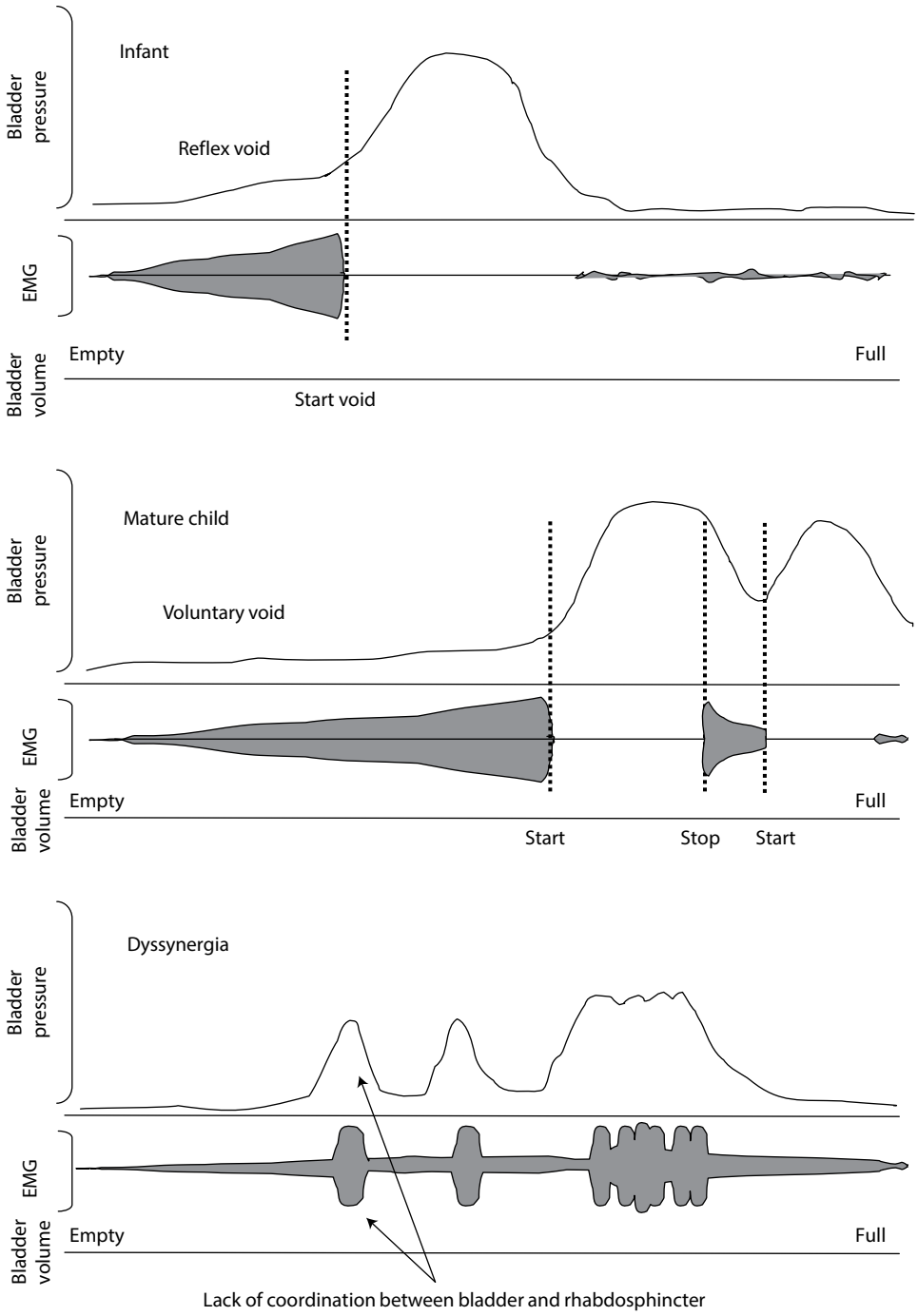

FIGURE 52.6 Schematic diagram showing the differences between infantile, mature child, and dyssynergic voiding, where there is a loss of coordination between the bladder and sphincter. The latter condition is often seen as a result of injury or disease to the CNS. Note that in both the infantile and mature child, there is coordination between the bladder and sphincter, so that the sphincter relaxes before the onset of bladder contraction, and the EMG becomes quiet. In the mature child and adult, there also exists the ability to interrupt voiding volitionally. When this happens, note that the sphincter activity precedes the cessation of bladder contractions, and when voiding is restarted, relaxation of the sphincter occurs before voiding is resumed. In contrast, in dyssynergia the detrusor and sphincter contract out of sequence, thereby working against each other.

injury or disease, simultaneous contraction of the bladder and rhabdosphincter can occur, leading clinically to DSD (Figure 52.6).[70]

Voiding is mediated by activation of the sacral parasympathetic efferent pathway to the bladder and the urethra along with reciprocal inhibition of the somatic pathway to the urinary sphincter. Cat studies reveal that the neurons in the brainstem have an essential role in the control of the parasympathetic component of voiding. Removal of the areas of the brain above the pons usually facilitates voiding by removing inhibitory inputs from higher centers. Transection at any point below abolishes micturition.

The region thereby isolated is the PMC. The PMC has been shown by physiologic and anatomic experiments to be the key switch in the voiding pathway. Chemical and electrical stimulation of the PMC in cats and dogs causes suppression of the urethral sphincter EMG activity, firing of the sacral PGNs, bladder contractions, and release of urine. These regions play a regulatory role, as shown by injections of the inhibitory transmitter, GABA, into the PMC of cats, which can increase the volume threshold for inducing micturition and, in high enough doses, completely block reflex voiding. In contrast, administration of a GABA inhibitor, such as bicuculline, can lower micturition volume threshold. Injuries above the lumbosacral area but beneath the PMC lead initially to an areflexic bladder and complete retention (similar to the spinal shock seen in human spinal cord injury patients) and later automatic micturition, but with bladder hyperactivity and DSD.[55,71]

The voiding reflex analogy to the guarding reflex is the urethra-to-bladder reflex.

Barrington first noted that flow of urine or mechanical stimulation of the urethra with a catheter would excite afferent nerves that can lead to bladder contractions in anesthetized cats.[72,73] It was hypothesized that the urethral-to-bladder reflex helps promote emptying. Two pathways have been identified. One is activated by somatic afferents in the pudendal nerve and needs facilitation from the PMC. The other uses afferents in the pelvic nerves to facilitate other spinal reflex mechanisms. Desensitizing the urethral afferents by capsaicin decreases this reflex. It is thought that this pathway may explain why stress and urge incontinence can occur together. The leakage of urine into the urethra triggers the reflex leading to urgency. Similarly, correction of stress incontinence has been observed to paradoxically improve detrusor instability.[65,74]

SPINAL AND SUPRASPINAL PATHWAYS

In the spinal cord, afferent pathways terminate and connect with second-order interneurons that relay information to the brain and to other regions of the spinal cord, including the preganglionic and motor nuclei at other levels. These are polysynaptic processes that interlink the various bladder, urethral, and sphincter reflexes. These interneuronal mechanisms play an important role in modulating lower urinary tract function.[75] The lower tract interneurons also receive afferent inputs from the bladder. Glutamic acid is the excitatory transmitter of these pathways.[74] About 15% of interneurons located medial to the SPN have inhibitory connections to the parasympathetic preganglionic nuclei. These inhibitory neurons use GABA and glycine.[74] Reflex pathways that control the external sphincter muscles also use glutamic excitatory and GABA or glycine inhibitory interneurons. The micturition reflex can be modulated at the spinal cord level by afferents from the cutaneous and striated muscle sources. Stimulation of afferent fibers can inhibit the firing of sacral interneurons evoked by bladder distention, which occurs as a result of presynaptic inhibition of primary afferents or due to direct postsynaptic inhibition of second-order neurons. Direct postsynaptic inhibition of bladder PGNs can occur by somatic afferent stimulation in the pudendal nerves. Suppression of bladder hyperactivity in patients with sacral root stimulation may reflect in part activation of the afferent limb of these inhibitory reflexes. This concept has been used to artificially modulate bladder behavior by sacral nerve stimulation.[76]

Control of bladder function starts in the higher cortical centers through the brainstem pons regions in the PMC and is mediated through the spinal cord nuclei to the efferent and afferent peripheral pathways. The micturition reflex is normally controlled and mediated by the pathway linking the brain with the reflexes described above. This pathway is termed the spinobulbospinal reflex pathway. Animal brain lesion studies show that the neurons in the brainstem at the level of the inferior colliculus have an essential role in the control of the parasympathetic component of micturition.[55] Decerebration above the colliculus facilitates micturition by eliminating inhibitory inputs from more cephalad centers. Transections below the colliculi abolish micturition. The essential control center thus isolated was found in the dorsal pontine tegmentum. First described in 1921, it is commonly referred to as the PMC or medial location.[77] The medial and lateral region of the pons is responsible for the micturition reflex. The medial region controls detrusor contraction via the reticulospinal tracts, which synapse with the preganglionic parasympathetic neurons in the sacral micturition center. Electrical stimulation of the medial region causes relaxation and opening of the urethral sphincter, followed within milliseconds by a contraction of the detrusor muscles.[78] The lateral regions of the PMC are connected via the corticospinal tracts to Onuf's nucleus. Electrical stimulation of this area leads to contraction of the rhabdosphincter. Voluntary control is via a link with the frontal cortex.[79,80] Neurons from the PMC project to the periaqueductal gray matter, thalamic nuclei, and limbic system. Neurons from the PMC communicate with supraspinal neuronal clusters that coordinate micturition with other functions. The location is of note because of two interesting neural topographic findings. First, the facial nerve nucleus is very near the PMC. Patients with Ochoa syndrome (urofacial syndrome) exhibit a combination of voiding dysfunction and a characteristic inversion of facial expression. No obvious structural lesion has ever been shown on imaging studies, but speculation suggests that there could be subtle synaptic or interneuron abnormalities.[81] Second, the nucleus locus ceruleus within the brainstem is a close neighbor of the PMC. The locus ceruleus in animals is activated by colonic stimulation. The PMC has been shown to affect the afferent signals from the pelvic viscera that reach the locus ceruleus. This has led to speculation that there may be bilateral interaction. Clinically, it has been observed that constipation and bowel dysfunction are associated with bladder dysfunction. It has been theorized that a local phenomenon, such as rectal distention impinging on the trigone or the pelvic nerves, may be responsible. This concept, however, fails to explain why women seem to be equally affected yet have the uterus and vagina "shielding" the bladder from the rectum. Perhaps the problem is at the central level due to interaction between the PMC and the locus ceruleus.[82,83]

The PMC has important direct synaptic inputs to the sacral PGNs and to the GABA-nergic neurons. The former carry excitatory outflow to the detrusor, whereas the latter act as an inhibitor on rhabdosphincter motor neurons. These reciprocal connections result in promoting bladder urethral sphincter synergy. Studies in rats indicate that activation of bladder PGNs from the PMC can be blocked by inotropic glutamate receptor antagonists, suggesting that neurons in the PMC utilize glutamate as a neurotransmitter.[70,84–86]

CENTRAL CEREBRAL PATHWAYS

Voluntary control of voiding is dependent on the connections between the frontal cortex and the septal or preoptic region of the hypothalamus, as well as connections between the paracentral lobule and the brainstem.[55] Lesions to those areas of cortex appear to directly increase bladder activity by removing cortical inhibitory control. Brain imaging by positron emission tomography (PET) has implicated the frontal cortex and anterior cingulate gyrus in the control of micturition, which is predominantly a right-sided function.[87,88] Since sacral parasympathetic pathways to the bladder form a predominantly positive feedback system, further inhibitory modulation is required to store urine and prevent early voiding. Higher centers, such as the cerebral cortex, cerebellum, basal ganglia, thalamus, and hypothalamus, thus play an inhibitory role in modulating the activity of the PMC.[89]

Studies in human beings indicate that voluntary control of micturition is dependent on connections between the frontal cortex and septal preoptic region of the hypothalamus and the paracentral lobule, brainstem, and spinal cord. Lesions in these areas due to trauma, tumors, or cerebrovascular disease appear to indirectly increase bladder activity by removing cortical inhibitory control. In cats, removal of the cortex lowers the functional bladder capacity. If the rest of the neuraxis is intact, removal of the cerebrum lowers the inhibitory input from the cortex. The hypothalamus plays a role in activating the sacral parasympathetic excitatory pathways, thereby inducing bladder contraction and voiding. It is thought to act either through direct inputs to the PMC and sacral micturition center or indirectly. This is not a unidirectional process. Modulating afferent inputs from the bladder are received by the hypothalamus. The gene *c-fos* has been identified as a marker for subsets of second-order neurons, as expression of *c-fos* has been found to increase in these neurons.[90,91]

PLASTICITY, MATURATION, AND REEMERGENCE

The neonatal bladder is not a fully functional storage organ. At birth, there is little cerebral input, and the bladder reflexively empties. In modern urodynamic parlance, a newborn through infancy and early toddler years has bladder overactivity. This is also seen in neonatal animals whose bladders show early spontaneous repetitive contractions. These early pathways do not disappear but rather become incorporated into more mature pathways by active inhibition from increasing cerebral maturation. Inhibition rather than cessation of these infantile reflexes is the important observation. Much as a layer of inhibition from the cerebrum modulates the spinal reflexes, a layer of inhibitory control is overlaid atop the neonatal reflexes. In newborn kittens and rats, a primitive reflex, the exteroceptive perineal-to-bladder reflex, is the principal voiding reflex until the mature spinobulbar or PMC-based reflex begins functioning at several weeks of life.[92] During the subsequent weeks, the adult-type voiding mediated by the micturition center and spinobulbospinal pathway becomes active, and the perineal-to-bladder reflex becomes progressively weaker and ultimately vanishes. Studies using pseudorabies virus tracing, cellular labeling, and CNS transection preparations in animals demonstrate that there is prominent reorganization of synaptic connections in the bladder reflex pathways.[93] At this time, the bulbospinal pathways that connect to the PMC are fewer and weaker. However, as the neonate matures, there is pruning of the interneuron to preganglionic synapses from the afferents and increased synapses from the bulbospinal pathways (Figure 52.7).[93,94] Interestingly, the higher pathways seem to be present and organized but inactive at birth. In animal studies, decerebration unmasks reflex bladder activity, which responds to bladder distention and is mediated by a supraspinal pathway. This indicates that supraspinal bladder-to-bladder reflexes are organized early after birth but are suppressed by inhibitory mechanisms within the brain. Postnatal development is associated with a marked reorganization of the circuitry of the CNS affecting micturition. The mechanism underlying the developmental suppression of the perineal-to-bladder reflex and the later reemergence after spinal cord injury appears to be similar to that of the maturation process. Downregulation occurs in the interneuronal to PGN excitatory synapses, possibly by synapse elimination due to competition for synaptic space between the boutons of the interneurons and the descending axons. Injury that causes degeneration of the descending axons, such as transection of the spinal cord, blocks this reorganization and maintains the primitive neonatal reflex. A similar degeneration of the descending axons in mature animals could stimulate axonal sprouting in interneuronal pathways and cause reemergence of the neonatal perineal-to-bladder reflex. While the details are not completely known, it is certain that remodeling of the interneuron to preganglionic synapses in the SPN has a prominent role. This synaptic plasticity and rearrangement lead to the downregulation of primitive spinal reflexes and the appearance of mature supraspinal control of voiding.[93]

Plasticity is therefore not a one-way process. Where inhibitory controls can be overlaid, they can also be removed. Disease processes can decrease or eliminate inhibitory influences, thereby unmasking the primitive neonatal reflexes. The urological sequelae of injury and disease, therefore, may not be a "new" change as much as an old reflex pathway that has reemerged. The classic example is the chilled water bladder test. Infants will develop involuntary bladder contractions when saline cooled to 4°C is instilled rapidly into the bladder. Mature children and adults can sense the cold but are able to maintain

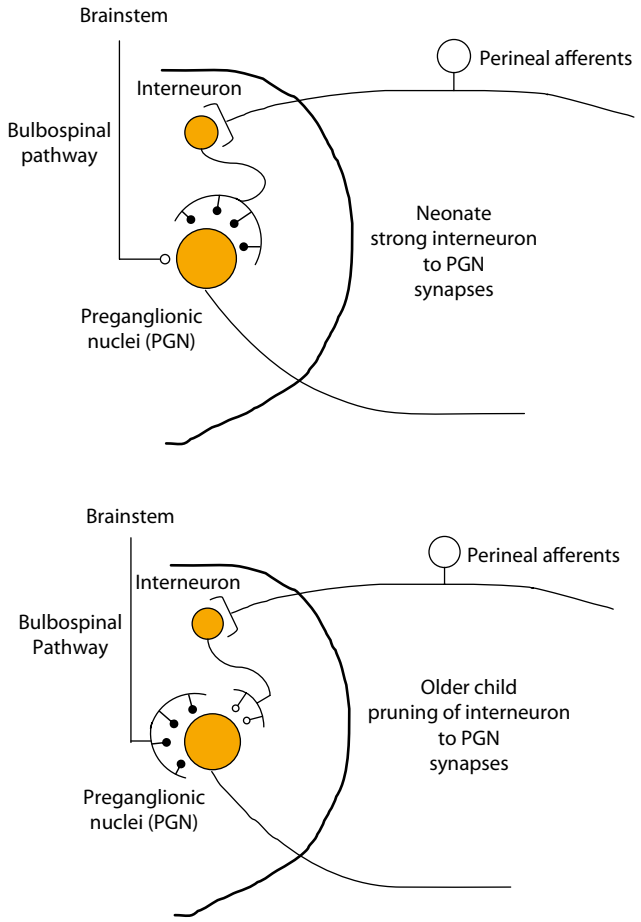

FIGURE 52.7 Schematic diagram showing possible anatomic changes at the synapses of the preganglionic nuclei in the sacral spinal cord of neonatal rats and kittens, which explain the changes during the first few weeks of life. Early in life, the interneurons bring greater active input (•) from the perineal afferents, but with maturation, these connections become pruned and downregulated (○). Input from the bulbospinal pathways then predominates.

control. Patients with neuropathic bladders are not able to do so. The cold receptors are mediated by C-fibers, and the chilled fluid response reflects unmasking of the neuropathology. It is positive until about age 4.[95,96] Further studies have shown that unmasking of reflexes can lead to structural changes that are not limited to the CNS and can occur in the periphery as well. In chronic spinal cord–transected cats, the afferent limb of the micturition reflex consists primarily of C-fiber afferents, whereas in intact cats, the pathways are myelinated alpha-delta afferents.[97]

Prior to maturation of the nervous system in the human fetus, urine is presumably eliminated by nonneural mechanisms. Later, voiding is initially regulated by a primitive reflex pathway organized in the spinal cord. As the CNS matures, this reflex voiding is eventually brought under voluntary control, which originates in the higher centers of the brain. As in animal models, a hierarchical control system overlays the more primitive components that are intrinsic to the target organs and spinal cord, as well as more complex components of the cerebral cortex. In adults, injuries and diseases of the CNS can lead to the reemergence of primitive functions that were suppressed during maturation.[98]

How do these observations correlate with the development of micturition control in humans? It appears that the process in humans does not occur suddenly. The process of maturation is not a simple switch from a primitive voiding reflex to the mature model but rather a gradual transition. Several observations support this viewpoint. First, small infants wake up to void when asleep.[99] By age 6 months, 90% of infants show signs of waking or arousal with voiding.[100] Another observation is that if an infant is disturbed while voiding, micturition halts or becomes interrupted. Longitudinal studies show increasing percentages of infants who arouse when voiding at night. This correlates with the degree of activation of cortical areas of the voiding reflex and to the degree of maturation.[99,100] Variable bladder volumes have also been noted, which causes doubt that threshold volume alone triggers voiding.[99–101] Interrupted voiding has been noted. This is defined as being two voids within 10 minutes. Seen in two-thirds of preterm and only one-third of full-term infants, it decreases over the first year and is not seen at all in the fully toilet-trained child. It is believed to be due to a form of DSD. Studies suggest that this dyssynergia may be a normal part of development.[102,103] There seem to be more interrupted voids in patients with posterior urethral valves (PUVs) and high-grade vesicoureteral reflux (VUR). Whether there is a more severe form of dyssynergia compared with the normal physiological form or an increase in hyperactivity of the neonatal detrusor is unclear. It also remains unknown if this observation has any relationship to bladder problems that can be associated with these conditions later in life (e.g., detrusor instability with VUR and myogenic detrusor failure with PUVs).[103,104] Increasing bladder capacity with age has been observed and leads to speculation that the stimulus for increasing bladder capacity is when the child begins to hold more urine at night, contrary to the conventional notion that daytime continence is a prerequisite for nighttime dryness.[101,102] Finally, increased hyperactivity is seen on cystometry during the first months of life and is felt to be a response to filling that is faster than normal and/or stimulus by the catheter. This fades as the neonate matures.[103] Increased reactivity of the detrusor may also be responsible for high voiding pressures. Voiding pressures of up to 100 cm H_2O have been measured in infants, which decreases to 70 cm H_2O by age 3 and continues to drop thereafter.[105]

These observations together suggest that the first few years of life mark an important transition period for infants and toddlers as they begin to shift over from a more primitive to a more mature micturition process. This transition seems to progress through a period where neither reflex pathway is clearly preeminent, thus explaining the higher voiding pressure, the hyperactive detrusor, and the period of physiologically normal DSD. The transition, therefore, in infants is not as abrupt and rapid as seen in animals. These findings and the earlier observation of the plastic nature of the micturition pathways and the reemergence of primitive pathways suggest that perhaps voiding dysfunction seen in childhood may have its roots in an incomplete transition to a more mature micturition pathway or the reemergence of the more primitive pathway.

Recent observations in the treatment of amblyopia ("lazy eye") suggest that plasticity may be dormant in adults and can be enhanced, trained, and perhaps induced pharmacologically. Originally, it was believed that if treatment (eye patching) were done too late (older than age 10 years), it would be ineffective because the brain would no longer be plastic enough to make the needed changes.[106] Reports of plasticity in adults with amblyopia challenged this long-held belief. Adults could experience spontaneous improvement of visual acuity in the amblyopic eye.[107,108] These studies are consistent with the notion that connections made early in life may be suppressed or inhibited and not destroyed. Brain plasticity in older children and adults may be more restricted because of physical and physiological "brakes" or limiters. Physical constraints from the myelin sheath restrict dendrite growth. Functional limiters may alter the balance between the excitatory and inhibitory stimuli to local neural circuits. The release of neurotransmitters like dopamine, serotonin, and norepinephrine could tilt the excitatory and inhibitory balance in favor of plasticity and overcome these limiters.[109,110] These observations lead to speculation that noninvasive induction or restoration of brain plasticity is possible even late in life by altering the balance of these excitatory and inhibitory neuromodulators. The treatment of amblyopia suggests two practical approaches to achieve this effect. First, rather than just depending on patching alone, systematic repeated eye exercises known as perceptual learning (PL) are prescribed. The use of PL has been shown to lead to improvement of overall acuity. Regular play of commercial off-the-shelf action video games can be more effective than the usual PL exercises.[111–113] Adults with amblyopia showed improvements of 13%–44% in visual acuity after regular play with their contralateral unaffected eye patched. There might be parallels to be drawn with the efforts to make biofeedback more effective by incorporating video games (see Chapter 55, Constipation and Lower Urinary Tract Symptoms).[114,115] The fundamental exercises (Kegel and others) of relaxing and contracting the pelvic muscles and urinary and anal sphincters are linked to visual goals and cues of a video game. This makes the process more fun for the patient but may promote this same plasticity effect. Second, it may be possible to reset plasticity by changing the excitatory and inhibitory balance pharmacologically. Chronic use of fluoxetine (Prozac™) has been shown to have an effect in adult rats with the murine equivalent of amblyopia.[116,117] This effect is believed to act on the Lynx1 mechanism. Lynx1 is a murine protein that appears to prevent plasticity in the primary visual cortex. Removing this molecular brake enhanced nicotinic ACh receptor signaling. Lynx1 expression is normally a positive factor by maintaining mature cortical networks in the presence of cholinergic innervation. Modulating the excitatory and inhibitory balance reactivates visual plasticity and may present a therapeutic target.[110]

CONCLUSIONS

Our understanding of the neurologic control of the storage and emptying of urine continues to deepen and broaden. Where once we only knew of a few neurotransmitters and a few basic reflex pathways, we now know of a dozen, along with their complex interplay. These pathways change with maturity but may never be completely lost. They may reemerge due to the plasticity of the nervous system. This plasticity may be a crucial target for future treatments and interventions for neurourologic conditions.

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CHAPTER
53

Neurogenic Voiding Dysfunction and Functional Voiding Disorders: Evaluation and Nonsurgical Management

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INTRODUCTION

Neurologic lesions that affect lower urinary tract (LUT) function cause at least 25% of the more severe clinical problems in pediatric urology. The advent of clean intermittent catheterization (CIC), introduced in the early 1970s by Lapides et al.,[1] and the refinements in techniques of urodynamic studies in children[2–4] dramatically changed the way these children were managed.[5] As a result, a greater understanding of the pathophysiology of the many diseases that primarily affect children, coupled with improved functional assessment of the LUT, has changed the treatment paradigm.[6,7] Now that it has been established that urodynamic studies can define children at risk for urinary tract deterioration, early aggressive and even proactive therapy have become the mainstay of management. Urodynamic testing is discussed in Chapter 51.

ASSESSMENT

All children with overt or suspected neuropathic bladder dysfunction (NBD) should undergo a thorough evaluation:

1. History
   a. Prenatal health
   b. Birth and development
   c. Perinatal complications
   d. Bowel and bladder habits
   e. Pattern of incontinence
   f. Bowel-emptying regimen
      i. Frequency, soiling
2. Physical examination
   a. Spine
   b. Lower extremities
      i. Deep tendon reflexes
      ii. Muscle mass and strength sensation
      iii. Gait
      iv. Perineal sensation, tone, reflexes
   c. Central nervous system (CNS)
      i. Handedness
      ii. Fine and gross motor coordination
3. Laboratory
   a. Urine analysis and culture
   b. Urine specific gravity
   c. Serum creatinine level
4. Radiography
   a. Renal and bladder sonography
   b. Voiding cystourethrography (VCUG)
   c. Spine radiograph—ultrasound, <3 months of age; magnetic resonance imaging (MRI), >3 months
5. Urodynamics
   a. Flow rate
   b. Residual urine (ultrasound or catheterized)
   c. Cystometrogram
   d. External urethral sphincter (EUS) electromyography (EMG)
   e. Static, filling, voiding urethral pressure profile

The history and physical examination are of paramount importance in the workup of children with NBD. The child's voiding habits prior to any injury and the current pattern of bladder emptying should be delineated. It is imperative to note whether the child voids voluntarily, spontaneously, or only with a Credé maneuver. Does the child have periods of dryness, or is there constant urinary leakage? Is the incontinence characterized by urgency and an inability to reach the toilet on time? Does the urine flow with a steady or intermittent stream or only dribble out during emptying? Does leakage occur with crying or laughing? Has the child had a urinary tract infection (UTI)? How much urine is produced each day? What is the pattern of bowel emptying? Is there fecal soiling?

Important components of the physical examination include an assessment of perianal and perineal sensation, anal sphincter tone, and the presence of bulbocavernosus and anocutaneous reflexes. Placing one's finger just at or slightly inside the external anal sphincter and briskly squeezing the glans penis or compressing the clitoris elicits the bulbocavernosus reflex. If the reflex is present, the external anal sphincter should contract. The anocutaneous reflex is elicited by scratching the pigmented skin directly adjacent to the anal opening, resulting in contraction of the perianal muscle. In children with

suspected NBD, complete evaluation of the back, including looking for agenesis of the sacrum, an abnormality of the gluteal cleft, or a cutaneous manifestation of an underlying occult spinal dysraphism, is important.[8–12] Examination of the lower extremities, comparing the muscle mass and strength of each leg, eliciting deep tendon reflexes, pinpointing sensory losses, and observing the gait may provide clues to the presence of an occult spinal dysraphism affecting not only the sacral but also the lumbar cord. Left-handedness in a family in which all members are right-handed, learning disabilities at school, poor fine and/or gross motor coordination, and attention deficit disorders all suggest the possibility of a central nervous disorder that might adversely affect LUT function.

CLASSIFICATION OF NEUROPATHIC BLADDER

The classification of NBD used in this chapter is that which has been adopted by the Urology Section of the American Academy of Pediatrics (AAP) in conjunction with the Urodynamic Society's classification, the International Continence Society (ICS),[13,14] and most recently, the International Children's Continence Society (ICCS).[15]

Under normal conditions, all portions of the LUT (detrusor, bladder neck, and EUS mechanism) function as a coordinated unit for adequate storage and efficient evacuation of urine. When a neurourologic lesion exists, these components usually fail to act in unison. A further refinement of the classification has been adopted based on dysfunction of a specific area of the vesicourethral unit and timing during the storage and/or voiding phase, rather than on a specific etiology:

1. Storage phase
   a. Detrusor tone
      i. Normal
      ii. Increased
         A. Detrusor overactivity (DO)
         B. Poor compliance
      iii. Diminished
         A. Good compliance
   b. Urethral closing mechanism
      i. Incompetent
         A. Bladder neck
         B. EUS
2. Voiding phase
   a. Detrusor contraction
      i. Normoactive
      ii. Underactive
         A. Unsustained
         B. Completely nonreactive
      iii. Overactive (highly contractile)
   b. Urethral closing mechanism
      i. Nonsynchronous (dyssynergic)
         A. Bladder neck
         B. EUS
      ii. Delayed opening
         A. Increased EMG lag time

Improper storage may be related to an alteration in detrusor function or an inadequate urethral closure mechanism. The bladder may have increased tone secondary to loss of muscle elasticity, and DO from excessive or unopposed sympathetic discharges, or due to a central lesion that prevents the normal inhibitory centers from influencing the sacral reflex arc. Incontinence may occur with any of these conditions despite a normal level of resistance in the bladder neck and urethra. Alternatively, incontinence may occur when the bladder neck and EUS areas do not provide adequate resistance during filling of the bladder or do not generate a reciprocal increase in outflow resistance as the bladder fills or abdominal pressure is raised. An injury to the spinal cord or nerve roots affecting the sympathetic, parasympathetic, or sacral somatic nervous system may alter both bladder neck and urethral sphincter tone. Periodic relaxation of the EUS during filling of the bladder, the result of loss of CNS inhibition, may also lead to urinary incontinence.

Incomplete evacuation of the bladder during the voiding phase may be due to an underactive detrusor muscle. A CNS lesion affecting the parasympathetic efferents may be responsible. However, nonsynchronous relaxation of the bladder neck or EUS area mechanisms (detrusor sphincter dyssynergia [DSD]) (Figure 53.1)[16] resulting from a lesion above the sacral cord, i.e., the pontine mesencephalic center or the cerebral cortex, can produce a similar effect. Myogenic failure occurs as the detrusor muscle hypertrophies, leading to DO, and then decompensates owing to persistent bladder outflow resistance. Eventually, this mechanism may produce overflow incontinence. Poor emptying can also occur as a result of delayed opening of the urethral sphincter. This abnormality manifests as an abnormally long lag time between voluntary detrusor contraction and pelvic floor relaxation, as seen on EMG.[17]

CONDITIONS: OVERVIEW

Congenital neurospinal dysraphisms (myelomeningocele, lipomeningocele, sacral agenesis, and other occult lesions) are the most common causes of NBD in children. However, a range of conditions can lead to pediatric NBD:

1. Neuropathic
   a. Spinal cord
      i. Congenital
         A. Neurospinal dysraphism
         B. Other anatomic
      ii. Acquired
         A. Trauma
         B. Tumor
         C. Infection
         D. Vascular
         E. Miscellaneous
   b. Supraspinal cord
      i. Anatomic or congenital
      ii. Trauma
      iii. Tumor
      iv. Infection
      v. Vascular

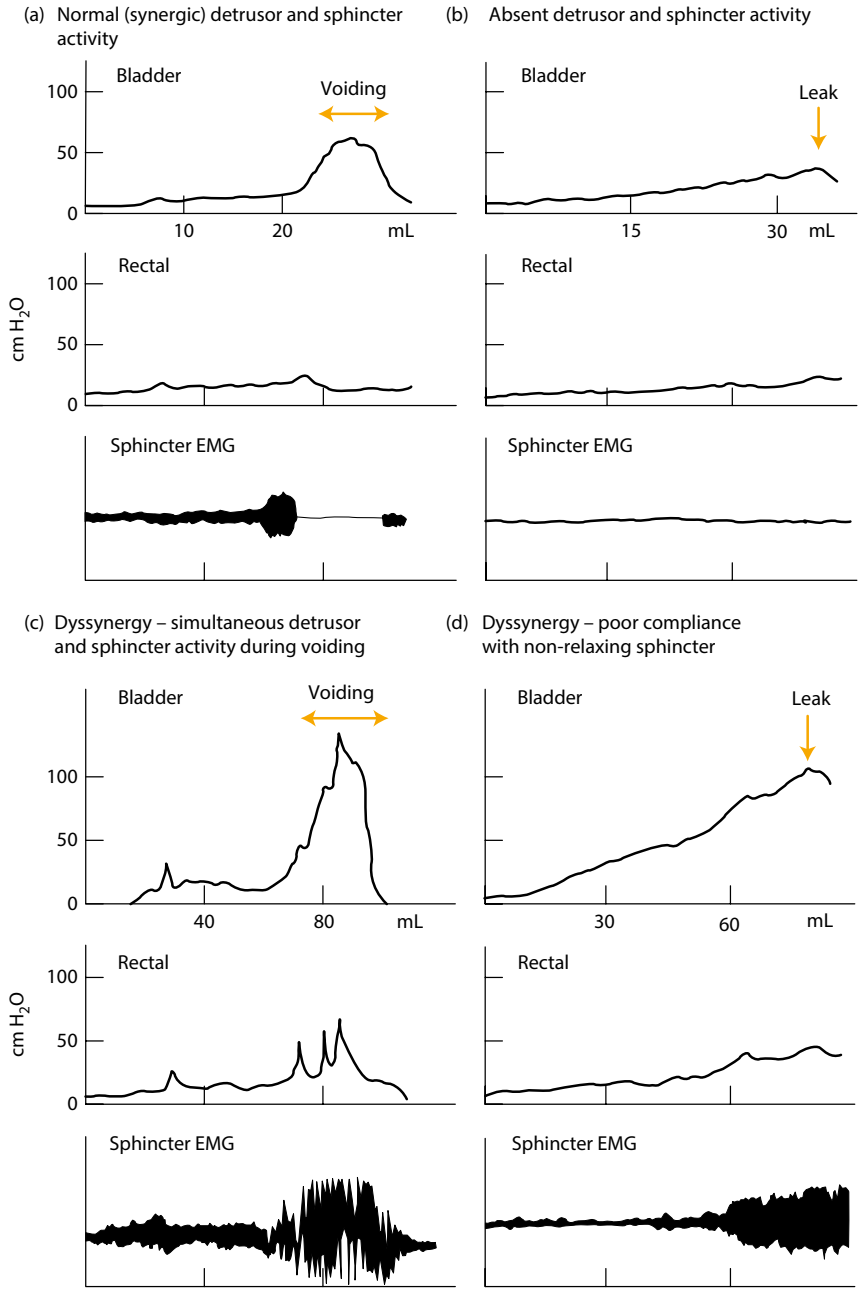

FIGURE 53.1 (a–d) Various patterns of urodynamic findings in newborns with myelodysplasia. Note that a hypertonic detrusor with a nonrelaxing sphincter (b) is also labeled dyssynergy. (Adapted from Bauer SB. Early evaluation and management of children with spina bifida. In King LR, ed., *Urologic Surgery in Neonates & Young Infants*. Philadelphia: Saunders, 1988, 252.)

vi. Degenerative
vii. Miscellaneous
viii. Temporary

c. Peripheral
i. Trauma
ii. Tumor
iii. Degenerative
iv. Guillain–Barré syndrome

2. Nonneuropathic
a. Anatomic
b. Myopathic
c. Psychological
d. Endocrinologic
e. Toxic

GENERAL TREATMENT STRATEGIES

Medical management of NBD regardless of etiology is based on the functional impairment produced by the specific neurologic defect:

1. DO or poor compliance
a. Oral anticholinergics—block detrusor cholinergic receptor sites

   b. Direct smooth muscle relaxants—relax detrusor
   c. Intradetrusor botulinum A toxin—inhibits acetylcholine release at the presynaptic cholinergic neuromuscular junction
   d. Urotherapy
2. Inadequate urethral resistance
   a. α-Sympathomimetics—stimulate bladder neck α_1 receptors to increase tone
   b. Dextronamer/hyaluronic acid injection—bladder neck bulking agent
   c. Urotherapy
3. Incomplete bladder emptying
   a. Cholinergic agonists—enhance detrusor contraction
   b. α-Sympatholytic agents—relax bladder neck
   c. Skeletal muscle relaxants—relax EUS
   d. EUS botulinum A toxin injection—relaxes EUS
   e. Urotherapy

Specific agents and typical doses are detailed in Table 53.1.

Lowering detrusor tone or abolishing overactive contractions with anticholinergics or direct smooth muscle relaxants aims to enhance inadequate storage capacity and decrease intravesical pressure. For patients refractory to oral agents, endoscopically injected botulinum A toxin (Botox™; Allergan, Inc.) may also be used. The effects of botulinum A are generally temporary, lasting approximately 6 months before repeat injection is necessary.[18,19] Our technique of Botox injection into the bladder is detailed in Video 53.1. Failure of conservative therapy to increase bladder capacity and lower detrusor tone results in the need for augmentation cystoplasty.

If inadequate urethral resistance is the primary reason for impaired storage of urine, the bladder neck mechanism, the EUS, or both, may be responsible. α-Sympathomimetics stimulate bladder neck α_1 receptors to enhance the tone of the muscles in this region. No drugs are commercially available that will increase the tone of denervated skeletal muscle in the EUS. The use of endoscopic bladder neck bulking agents, including dextronamer/hyaluronic acid (Deflux™; Salix Pharmaceuticals, Inc.), has also been described,[20–24] although results are mixed and incontinence due to low outlet resistance often ultimately requires surgical management.[25]

Incomplete emptying of the bladder may be due to an underactive bladder, unsustained detrusor contractions, or uncoordinated activity at the bladder neck and/or EUS. α-Sympatholytic agents or skeletal muscle relaxants may facilitate emptying. Although conflicting reports have been published regarding the efficacy of bethanechol, it does seem to improve emptying of the bladder in most instances.[26,27] Bethanechol (Urecholine™; Teva Pharmaceuticals) should be administered with α-sympatholytic agents because it also increases urethral resistance at the bladder neck. For patients who fail α-sympatholytic therapy, injection of botulinum A toxin into the EUS has been reported, with promising results.[28]

For children with functional causes of DO and/or incomplete emptying, urotherapy is the mainstay of treatment and pharmacologic therapies are largely adjunctive. The functional voiding disorders and their treatments are discussed in detail toward the end of the chapter.

NEUROSPINAL DYSRAPHISMS

Myelodysplasia

The most common etiology of NBD in children is abnormal spinal column development. During normal fetal maturation, the spinal canal closes cranially to caudally, completing the process by 35 days' gestation. Although the exact mechanism causing dysraphism is unknown, numerous factors, including genetic influences,[29,30] have been implicated. The incidence is estimated at 1 in 1000 births in the United States,[31] but there has been a decrease in this occurrence.[32] Two explanations are possible: first, with the advent of prenatal screening, many families are electing to terminate their pregnancies when they have affected fetuses,[33] and second, *the addition of folic acid supplements to the diet of women of childbearing age has reduced the incidence of spina bifida by more than 50%*.[34,35] If spina bifida is already present in one member of a family, there is a 2%–5% chance of a second sibling being born with the same condition.[36] The incidence doubles when more than one family member has a neurospinal dysraphism (Table 53.2).

Pathogenesis

Myelodysplasia is an all-inclusive term used to describe several abnormalities of the vertebral column. More specific labels regarding each abnormality include

- *Meningocele*: Just the meninges extend beyond the confines of the vertebral canal without any neural elements within it.
- *Myelomeningocele*: Neural tissue (nerve roots and/or portions of the spinal cord) has evaginated with the meningocele.
- *Lipomyelomeningocele*: Fatty tissue has developed with the cord structures, and both are protruding into the sac.

Myelomeningocele accounts for >90% of all the open spinal dysraphic states.[37] Most spinal defects occur at the level of the lumbar vertebrae, with the sacral, thoracic, and cervical areas being affected in decreasing order of frequency (Table 53.3).[38] In 85% of affected children, an associated Arnold–Chiari malformation is present; in such cases, the cerebellar tonsils have herniated to a variable degree down through the foramen magnum, obstructing the fourth ventricle, thus preventing cerebral spinal fluid from entering the subarachnoid space surrounding the brain and spinal cord.

The neurologic lesion produced by this condition is variable depending on which neural elements have protruded with the meningocele sac. The bony vertebral level often gives little or no clue as to the level of neurologic deficits. The height of the bony level and the highest extent of the neurologic lesion may vary from one to three vertebrae in each direction.[39] There may be differences in function from one side of the body to the other at the same neurologic level, and from one neurologic level to the next, as a result of asymmetry of affected neural elements. Children with thoracic and upper lumbar meningoceles often have complete reconstitution of their spine in the sacral area

TABLE 53.1 Oral (a) and endoscopic (b) therapy for neuropathic bladder dysfunction

(a) Type	Minimum dosage	Maximum dosage
Cholinergic		
Bethanechol (Urecholine; Teva Pharmaceuticals)	0.7 mg/kg tid	0.8 mg/kg qid
Anticholinergic		
Propantheline (Pro-Banthine; RPG Life)	0.5 mg/kg bid	0.5 mg/kg qid
Oxybutynin (Ditropan; Janssen Pharmaceuticals)	0.2 mg/kg bid	0.2 mg/kg qid
Glycopyrrolate (Robinul; Shionogi)	0.01 mg/kg bid	0.03 mg/kg tid
Hyoscyamine (Levsin; Alaven Pharmaceutical, LLC)	0.003 mg/kg bid	0.01 mg/kg qid
Tolteridine (Detrol; Pfizer)	0.03 mg/kg bid	0.1 mg/kg bid
Trospium (Sanctura; Allergan)	0.1 mg/kg bid	0.5 mg/kg bid
Darifenacin (Enablex; Novartis Pharmaceuticals Corp.)	0.1 mg/kg qd	0.5 mg/kg qd
Fesoterodine (Toviaz; Pfizer)	0.03 mg/kg qd	0.1 mg/kg qd
Solifenacin (Vesicare; Astellas Pharmaceuticals, Inc.)	0.05 mg/kg qd	0.3 mg/kg qd
Sympathomimetic		
Phenylpropanolamine (alpha) (Ornade; GlaxoSmithKline Pharmaceuticals, Inc.)	2.5 mg/kg bid	2.5 mg/kg tid
Ephedrine (alpha)	0.5 mg/kg bid	1.0 mg/kg tid
Pseudoephedrine (alpha) (Sudafed; Johnson & Johnson)	0.4 mg/kg bid	0.9 mg/kg tid
Sympatholytic		
Prazosin (alpha) (Minipress; Pfizer)	0.05 mg/kg bid	0.1 mg/kg tid
Phenoxybenzamine (alpha)	0.3 mg/kg bid	0.5 mg/kg tid
Propranolol (beta)	0.25 mg/kg bid	0.5 mg/kg bid
Doxazosin (alpha) (Cardura; Pfizer)	0.01 mg/kg qd	0.02 mg/kg qd
Smooth muscle relaxant		
Flavoxate (Urispas; GlaxoSmithKline Pharmaceuticals, Inc.)	3.0 mg/kg bid	3.0 mg/kg tid
Dicyclomine (Bentyl; Aptalys Pharmaceutical Technologies)	0.1 mg/kg tid	0.3 mg/kg tid
Other		
Imipramine (Tofranil; Covidien)	0.7 mg/kg bid	1.2 mg/kg tid
(b) Type	**Typical dosage**	
Anticholinergic—detrusor		
Botulinum toxin A (Botox; Allergan, Inc.)	10–12 IU/kg, up to a maximum of 300 IU	
Anticholinergic—sphincter		
Botulinum toxin A (Botox; Allergan, Inc.)	50–100 IU	
Bladder neck bulking agent		
Dextronamer/hyaluronic acid (Deflux; Salix Pharmaceuticals, Inc.)	1–10 mL	
Subureteric injection for reflux		
Dextronamer/hyaluronic acid (Deflux; Salix Pharmaceuticals, Inc.)	1–2 mL/ureter	

and will frequently have intact sacral reflex arc function. In fact, it is more likely for children with upper thoracic or cervical lesions to have just a meningocele and no myelocele, with no demonstrable loss of function. Finally, the differential growth rates between the vertebral bodies and the elongating spinal cord add a factor of dynamicism in the developing fetus that further complicates the picture.[40] Superimposed on all this is the Arnold–Chiari malformation, which may have a profound effect on the brainstem and pontine center involved in the control over LUT function.

Given this complicated anatomic relationship, LUT function is affected in a variety of ways and cannot be predicted just by looking at the spinal abnormality or the neurologic function of the lower extremities. This wide spectrum of dysfunction is evident when examining babies with sacral-level lesions.[41] Even careful assessment of the sacral area may not provide sufficient information to make

TABLE 53.2 Familial risk of myelodysplasia in the United States per 1000 live births

Relationship	Incidence
General population	0.7–1.0
Mother with one affected child	30–50
Mother with two affected children	100
Patient with myelodysplasia	40
Mother older than 35 years	30
Sister of mother with affected child	10
Sister of father with affected child	3
Nephew who is affected	2

Source: Adapted from Kroovand RL et al. Myelomeningocele. In Campbell MF, Walsh PC, eds., *Campbell's Urology*, 5th edn. Philadelphia: Saunders, 1986, 2193.

TABLE 53.3 Spinal level of myelomeningocele

Location	Incidence (%)
Cervical—high thoracic	2
Low thoracic	5
Lumbar	26
Lumbosacral	47
Sacral	20

Source: Adapted from Kroovand RL et al. Myelomeningocele. In Campbell MF, Walsh PC, eds., *Campbell's Urology*, 5th edn. Philadelphia: Saunders, 1986, 2193.

a concrete inference. Therefore, urodynamic evaluation in the neonatal period is now standard. Urodynamics provide a clear picture of the function of the sacral spinal cord and LUT that helps predict risk for future urinary tract deterioration.[6,7,41–44]

Newborn Assessment

Ideally, urodynamic testing would occur immediately after the baby is born, but the risk of spinal infection and the urgency for closure have not made this a viable option. A 1990 study showed that fewer than 5% of children experience a change in their neurologic status as a result of the spinal canal closure.[45] Therefore, renal ultrasonography and a measurement of residual urine are performed as early as possible postnatally, with urodynamics delayed until it is safe to transport children and place them on their backs or sides for the test. For infants who cannot empty completely, CIC is begun, even before urodynamic testing. The normal bladder capacity in the newborn period is between 10 and 15 mL; thus, an acceptable residue of urine is <5 mL. Urine analysis and culture and serum creatinine should also be evaluated in the newborn.[46] Once the spinal closure has healed sufficiently, renal scintigraphy is performed to assess upper urinary tract function and drainage. VCUG is conducted if there is hydronephrosis and/or the urodynamic study demonstrates risk factors for upper urinary tract deterioration. Thus, urodynamics fulfill multiple objectives:[6,7,43,47]

1. They provide baseline information about the radiologic appearance of the upper and lower urinary tract, as well as the condition of the sacral spinal cord and the CNS.
2. They can be compared with later assessments, so that early signs of urinary tract deterioration or of progressive neurologic denervation can be detected.
3. They help to identify babies at risk for urinary tract deterioration as a result of poor compliance or outflow obstruction from DSD, which then allows prophylactic measures to be initiated before the changes actually take place.
4. They help the physician to counsel parents with regard to their child's future bladder and sexual function.

Findings

Ten to fifteen percent of newborns have an abnormal radiographic appearance to their urinary tract when first evaluated;[48] 3% have hydroureteronephrosis secondary to spinal shock, probably from the closure procedure,[49] whereas 10% have abnormalities that developed in utero as a result of abnormal LUT function in the form of bladder outlet obstruction (BOO).

Urodynamic studies in newborns have shown that 57% of infants with myelomeningocele have bladder contractions. This is especially true in children with upper lumbar or thoracic lesions who have sparing of the sacral spinal cord, 83% of whom have detrusor contractions.[50] Forty-three percent have an underactive bladder, and compliance during bladder filling is either good (25%) or poor (18%) in this subgroup.[7] EMG assessment of the EUS demonstrates an intact sacral reflex arc with no evidence of lower motor neuron (LMN) denervation in 47% of newborns, whereas partial denervation is seen in 24% and complete loss of sacral cord function is noted in 29%.[51] One recent study suggested that a higher degree of cerebellar herniation on MRI was associated with more severe postnatal bladder function.[52]

Combining bladder contractility and EUS activity results in three categories of LUT dynamics: synergic; dyssynergic, with and without poor compliance; and complete denervation (Figure 53.1).[7,43] Synergy is characterized by complete silencing of the sphincter during a detrusor contraction or when capacity is reached at the end of filling. Voiding pressures are usually within the normal range. Dyssynergy occurs when the EUS fails to decrease, or increases its activity during a detrusor contraction or a sustained increase in intravesical pressure, during bladder filling.[53] Frequently, a poorly compliant bladder with high intravesical pressure is seen in conjunction with DSD, resulting in a bladder that empties only at high intravesical pressure.[42,43] Complete denervation is noted when no bioelectric potentials are detectable in the region of the EUS at any time during the micturition cycle or in response to a Credé maneuver or sacral reflex stimulation.

Categorizing LUT function in this way is useful because it defines which children are at risk for urinary

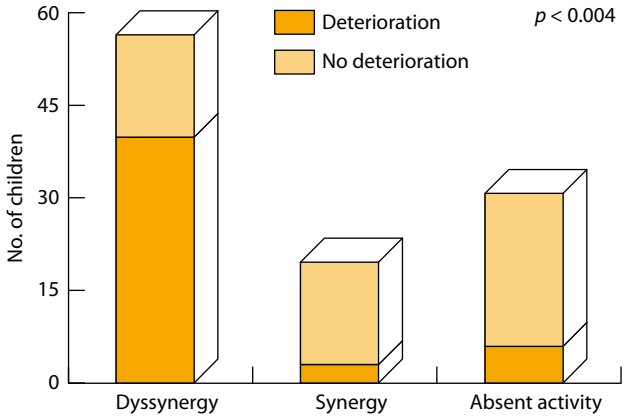

FIGURE 53.2 Urinary tract deterioration is related to outflow obstruction and most often associated with dyssynergy. Children with synergy converted to dyssynergy and patients with complete bladder denervation developed fibrosis with a fixed high-outlet resistance in the external sphincter, before any changes occurred in the urinary tract. (Adapted from Bauer SB. Early evaluation and management of children with spina bifida. In King LR, ed., *Urologic Surgery in Neonates & Young Infants*. Philadelphia: Saunders, 1988, 252.)

tract changes, which should be treated prophylactically, which need close surveillance, and which can be followed at greater intervals without fear of deterioration. On initial assessment or subsequent studies, 71% of newborns with DSD had urinary tract deterioration within the first 3 years of life, whereas only 17% of synergic voiders and 23% with a completely denervated sphincter developed similar changes (Figure 53.2). When the upper urinary tract of the infants in the synergic group deteriorated, it did so only after the infants converted to a dyssynergic pattern. Among the infants with complete denervation, the only babies with hydronephrosis were those who had elevated levels of urethral resistance, presumably due to fibrosis of the skeletal muscle component of the EUS. Thus, it appears that BOO is a major contributor to the development of urinary tract deterioration in these children (Figure 53.3). Bladder tonicity plays an important but somewhat less critical role in this regard,[6] although detrusor compliance seems to be worse in children with high levels of outlet resistance.[54] This combination of parameters (poor compliance and high outlet resistance) is very provocative for the development of hydroureteronephrosis,[55,56] whereas DSD is a significant factor in the onset of vesicoureteral reflux (VUR) (Figure 53.3).[57] First Bloom and associates[58] and then Park and associates[59] noted an improvement in compliance when outlet resistance was lowered following gentle urethral dilation in these children; however, the reasons for this are unclear and the long-term effect of this maneuver on ultimate continence and upper urinary tract function remains uncertain.

Specific Recommendations

Because expectant treatment has revealed that infants with BOO due to DSD or denervation fibrosis are at considerable risk for urinary tract deterioration, the idea of prophylactically treating the children has emerged as an important alternative to expectant therapy. When CIC is initiated in newborns, it becomes easy for parents to master, even in uncircumcised boys, and for children to accept as they grow older.[60] Complications of meatitis, epididymitis, or urethral injury are rare, and symptomatic UTI occurs in fewer than 30%,[61] although asymptomatic bacteriuria can be seen in almost 70%.[62]

CIC alone or in combination with anticholinergic agents, when detrusor filling pressures are >40 cm H_2O and voiding pressures reach levels of >80–100 cm H_2O, has resulted in only an 8%–10% incidence of urinary tract deterioration (Figure 53.4).[61,63,64] This represents a significant

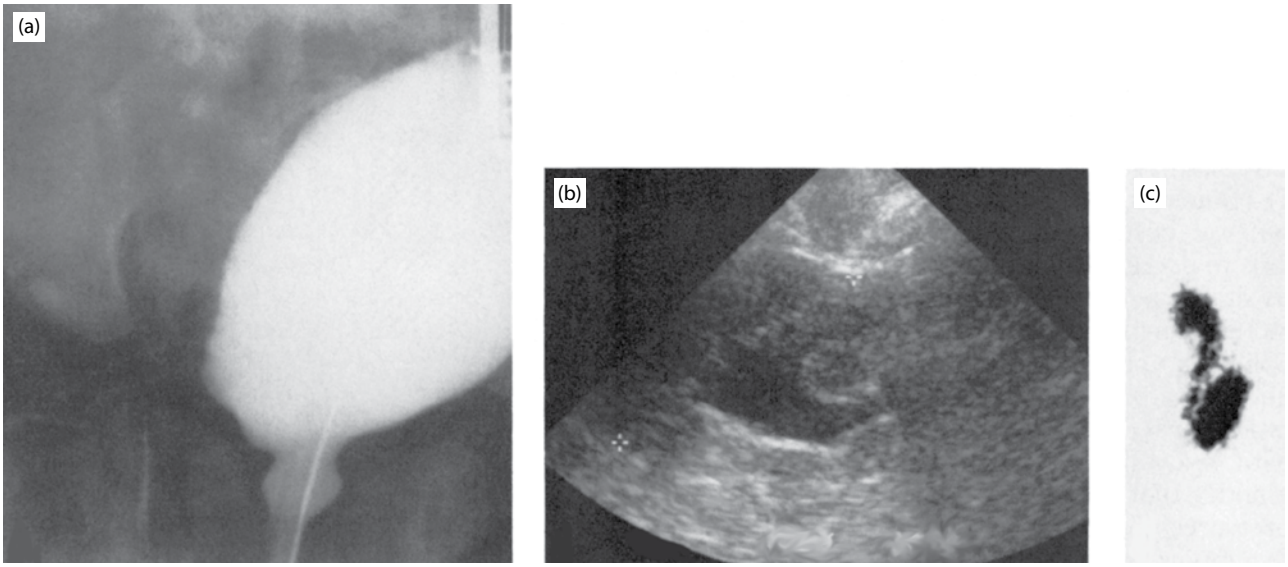

FIGURE 53.3 (a) VCUG in a newborn girl with dyssynergy and elevated voiding pressures demonstrated no reflux and a smooth-walled bladder. Her initial renal echogram was normal. She was started on CIC and oxybutynin (Ditropan) but did not respond. Within 1 year, she had right hydronephrosis (b) and severe reflux on a radionuclide cytogram (c).

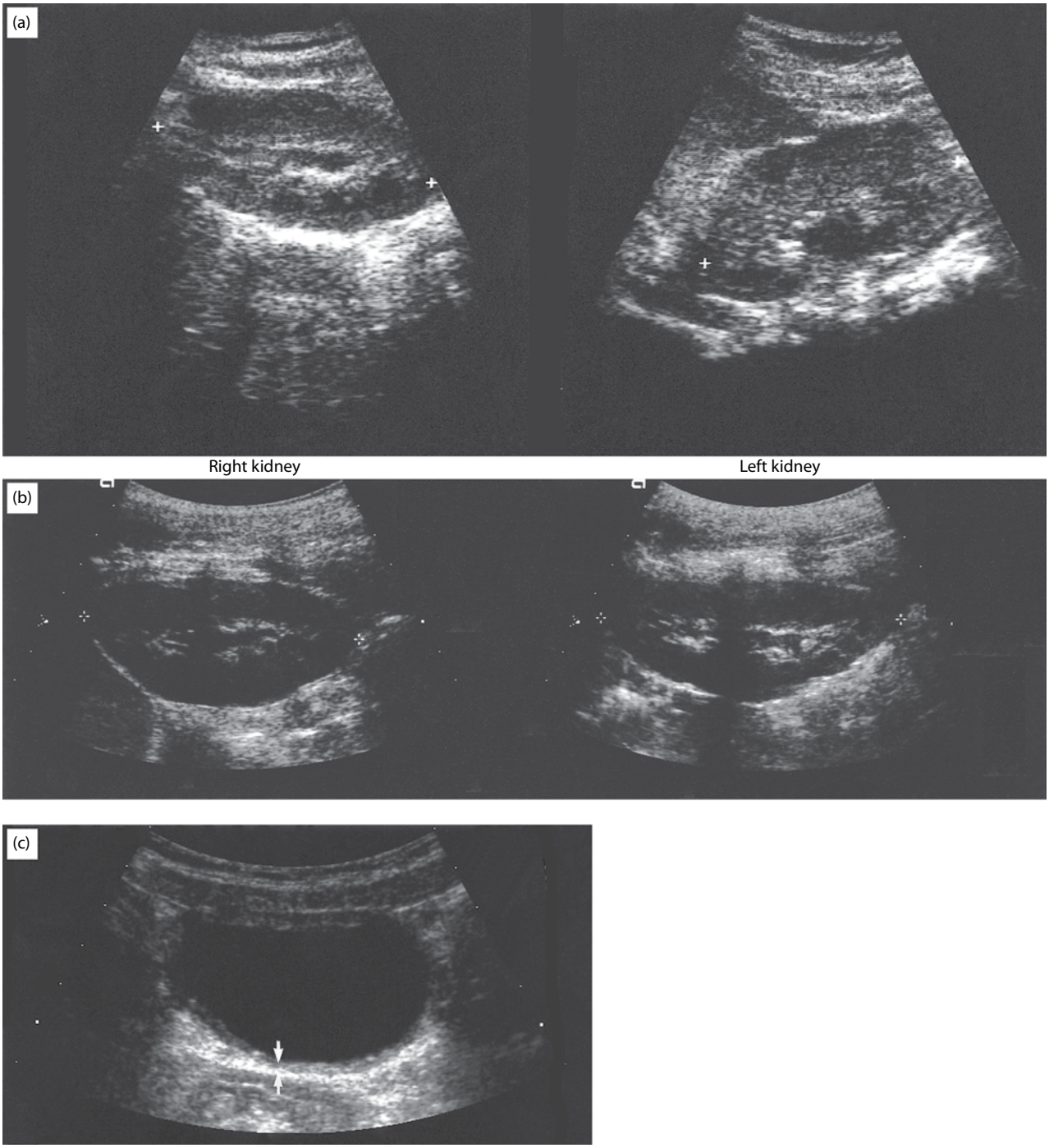

FIGURE 53.4 A newborn boy with DSD was successfully treated with CIC and oxybutynin. Over a 14-year period, his kidneys have remained normal by renal ultrasound (a and b) and his bladder wall has not increased its thickness (c).

drop in the occurrence of detrimental changes compared with children followed expectantly.[6,7,43] For infants, oxybutynin is administered in a dose of 1.0 mg/year of age, every 12 hours, in order to help lower detrusor filling pressure. In neonates or children younger than 1 year of age, the dose is lowered to below 1.0 mg in relation to the child's age at the time and increased proportionately as the child approaches 1 year. Subsequent management should be guided by the pattern of NBD, as detailed earlier in the chapter.

Follow-Up

The neurourologic lesion in myelodysplasia is dynamic with changes taking place throughout childhood,[65–67] especially in early infancy,[51] and then at puberty,[68] when the linear growth rate accelerates again. When a change is noted on neurologic, orthopedic, or urodynamic assessment, radiologic investigation of the CNS often reveals (1) tethering of the spinal cord, (2) a syrinx or hydromyelia of the cord, (3) increased intracranial pressure due to a shunt

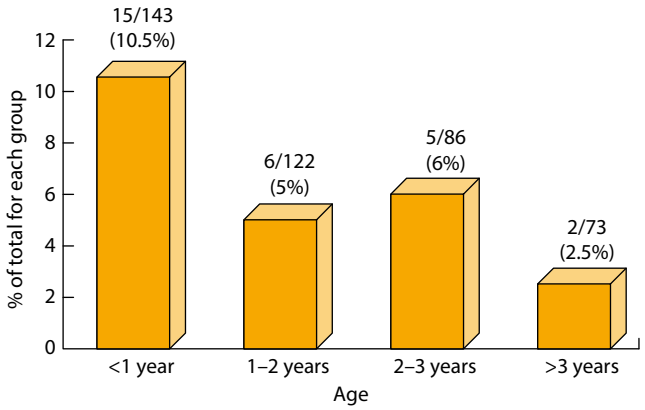

FIGURE 53.5 Propensity for deterioration in EUS innervation is greatest in the first year of life, with a decreasing incidence noted subsequently. (Adapted from Bauer SB. Early evaluation and management of children with spina bifida. In King LR, ed., *Urologic Surgery in Neonates & Young Infants*. Philadelphia: Saunders, 1988, 252.)

malfunction, or (4) partial herniation of the brainstem and cerebellum. Children with completely intact or only partially denervated sacral cord function are particularly vulnerable to progressive changes.

Most children who change tend to do so in the first 3 years of life (Figure 53.5). Thus, yearly urodynamics from birth to 5 years of age provide the means for carefully following children to detect signs of change, offering the hope that early detection and neurosurgical intervention may help to arrest or reverse a progressive pathologic process. All babies with myelodysplasia should be observed according to the guidelines set forth in Table 53.4. Urodynamics should also be repeated when the upper urinary tract dilates secondary to impaired drainage from a hypertonic detrusor, recurrent UTIs develop, or incontinence occurs after a prolonged period of dryness.

TABLE 53.4 Surveillance in infants with myelodysplasia[a]

Sphincter activity	Recommended tests	Frequency
Intact—synergic	Postvoiding residual	Every 4 months
	Renal ultrasound	Every 12 months
	UDS	Every 12 months
Intact—dyssynergic[b]	Renal ultrasound	Every 12 months
	UDS	Every 12 months
	VCUG or RNC[c]	Every 12 months
Partial denervation	Postvoiding residual	Every 4 months
	Renal ultrasound	Every 12 months
	UDS[d]	Every 12 months
	VCUG or RNC[c]	Every 12 months
Complete denervation	Postvoiding residual	Every 6 months
	Renal ultrasound	Every 12 months

Abbreviations: UDS, urodynamic study; RNC, radionuclide cystography.
[a] Until the age of 5 years.
[b] Patients on intermittent catheterization and anticholinergic agents.
[c] If detrusor hypertonicity or reflux already present.
[d] Depending on degree of denervation.

Management of Reflux

VUR occurs in 3%–5% of newborns with myelodysplasia, usually in association with poor compliance and/or dyssynergia.[63,69] If left untreated, the incidence of reflux in these at-risk infants increases with time until 30%–40% are afflicted by 5 years of age,[69] with even higher levels noted in older children.[57]

In children with mild to moderate reflux (I–III), who void spontaneously, or who have complete lesions with little or no outlet resistance and empty their bladder completely, management consists of antibiotic prophylaxis to prevent recurrent infection. Children with high-grade reflux (grade IV or V) and/or who cannot empty their bladders spontaneously, regardless of the grade of reflux, undergo CIC to ensure complete emptying. Children with DO, with or without hydroureteronephrosis, are also treated with anticholinergics to lower intravesical pressure and ensure upper urinary tract decompression. This strategy results in reflux resolution in 30%–55% and preserved renal function.[60,69–73] Although bacteriuria can be seen in as many as 56% of children on CIC, generally it is not harmful except in the presence of high-grade reflux because symptomatic UTI and renal scarring rarely occur with low-grade VUR.[70,74]

Credé voiding is to be avoided in children with reflux and a reactive EUS. Under these conditions, Credé results in a reflex response of the EUS that increases urethral resistance and raises the pressure needed to expel urine from the bladder (Figure 53.6).[75] This aggravates the degree of reflux and increases upper urinary tract dilation. Vesicostomy drainage[8,76] is reserved for children (1) who have such severe reflux that CIC and anticholinergic medication fail to improve upper urinary tract drainage, or (2) whose parents cannot adapt to the catheterization program.

The indications for antireflux surgery are similar to those for children with normal bladder function and include recurrent symptomatic UTI while on adequate antibiotic therapy and appropriate catheterization techniques, persistent hydroureteronephrosis despite effective emptying of the bladder and lowering of intravesical pressure, severe reflux with an anatomic abnormality at the ureterovesical junction, and reflux persisting into puberty. In addition, children with any grade of reflux who are being considered for implantation of an artificial urinary sphincter or another procedure designed to increase bladder outlet resistance should have the reflux corrected at the time of or prior to the anti-incontinence surgery.

Jeffs et al.[77] noted that antireflux surgery could be very successful in children with NBD as long as it is combined with measures to ensure complete bladder emptying. Since the advent of CIC, success rates for antireflux surgery have approached 95%.[70,78–80] Unilateral reflux does not warrant bilateral reimplantation, because the incidence of contralateral reflux postoperatively is insignificant.[79] The endoscopic injection of dextronamer/hyaluronic acid has altered the management of reflux in children with myelomeningocele, but long-term salutary effects are yet to be appreciated.[81,82]

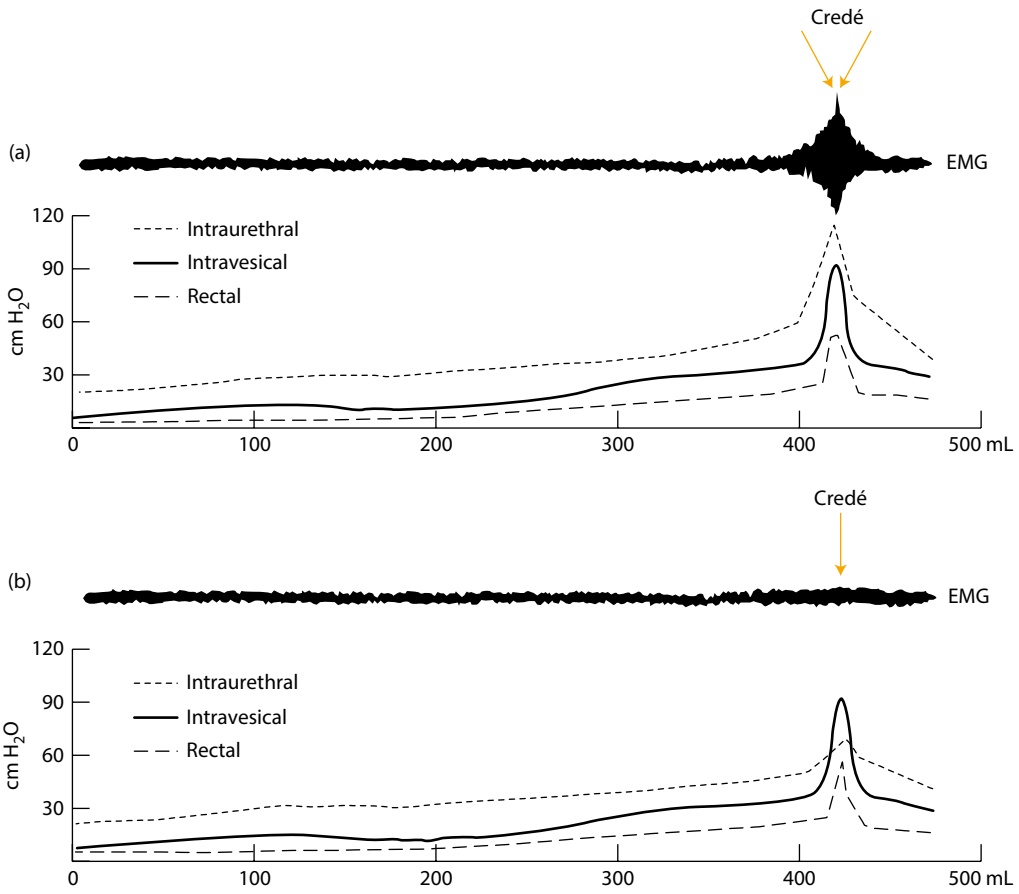

FIGURE 53.6 (a) When the external sphincter is reactive, a Credé maneuver produces a reflex increase in EMG activity of the sphincter and a concomitant rise in urethral resistance, resulting in high voiding pressure. (b) A child whose sphincter is denervated and nonreactive will not have a corresponding rise in EMG activity, urethral resistance, or voiding pressure. A Credé maneuver here will not be detrimental. (Adapted from Bauer SB. Early evaluation and management of children with spina bifida. In King LR, ed., *Urologic Surgery in Neonates & Young Infants*. Philadelphia: Saunders, 1988, 252.)

Continence

Urinary and fecal continence are becoming increasingly important issues to address at an early age as we strive to help children with myelodysplasia adapt socially. Initial attempts at achieving urinary continence include CIC and drug therapy designed to maintain low intravesical pressure and a reasonable level of urethral resistance. Although this approach can be administered on an empiric basis, it is more efficient to determine treatment protocols based on urodynamic findings. As a result, urodynamic testing is performed if initial attempts with CIC and oxybutynin fail to achieve continence.

Urodynamic findings guide further therapy, as detailed in the "General Treatment Strategies" section earlier in this chapter.

Fecal continence is also an important social issue for children with myelomeningocele, especially as they reach adolescence.[83] In addition to dietary maneuvers, intravesical bladder stimulation has helped with fecal continence,[84] but the most impressive results have come from the Malone antegrade continence enema (MACE) procedure. A continent catheterizable conduit is created from the colon to the anterior abdominal wall using the appendix or a narrowed reconfigured segment of bowel. The cecal end of the conduit is implanted in such a manner as to prevent leakage. An enema solution consisting of either GoLYTELY™, saline, or tap water is instilled nightly or every other night, cleansing the distal bowel within a short time, and resulting in fecal continence for up to 2–3 days at a time. Although equal continence rates have been observed with antegrade and retrograde enemas,[85] the MACE allows older children to become independent in managing their bowel function, which leads to improved self-esteem and social functioning.[86,87] Despite the advantages and promise of the MACE procedure, stomal complications and reoperations are common, a risk that patients and families should understand from the outset.[88,89]

Sexuality

Sexuality in this population has become an increasingly important issue to address as more individuals reach adulthood and desire marriage or other meaningful long-term romantic relationships.[90] Few studies are available, however, that critically evaluate sexual function in these patients.

In one study, researchers interviewed a group of affected teenagers and reported that at least 28% of them had one or more sexual encounters, and almost all had a desire to marry and ultimately bear children.[90] In another study,[91]

57 men were questioned regarding their sexual history: 41 (72%) had erections and 27 of them (66%) had ejaculations. Twenty men said they had had sexual intercourse, but only 11 attempted to father children, of whom 8 were successful. Overall, 12 men (21%) were married. Another study revealed that 70% of myelodysplastic women were able to become pregnant and have an uneventful pregnancy and delivery, although urinary incontinence in the latter stages of gestation and cesarean section were common.[92] In the same study, 17% of males claimed that they were able to father children. It is more likely for males to have problems with erectile and ejaculatory function because of the frequent neurologic involvement of the sacral spinal cord, whereas reproductive function in the female, which is under hormonal control, is not affected. However, the level of the neurologic lesion is not completely predictive of ultimate sexual function in men.[91]

In addition to understanding what the precise anatomical sexual function is in an individual, understanding the individual's sexuality as the ability to interact with a partner in a fulfilling and lasting way is just as important. Sexual identity, education, and social mores are issues that have been taken out of the realm of secrecy and are now openly discussed with and taught to patients with myelodysplasia,[93–96] although relatively few patients receive sex education specific to individuals with their condition.[97] Boys reach puberty at an age similar to that for normal males, whereas breast development and menarche tend to start as much as 2 years earlier than usual in myelodysplastic females. The etiology of this early hormonal surge is uncertain, but it may be related to pituitary function changes in girls secondary to their hydrocephalus.[98] The degree of sexuality attained by most is inversely proportional to the level of neurologic function; a lower lesion level has been correlated with a greater likelihood of sexual activity.[99] Note that the level of lesion does not correlate with the degree of sexual satisfaction in patients with myelodysplasia.[100]

Lipomeningocele and Other Spinal Dysraphisms

Diagnosis

A group of congenital defects that affects formation of the spinal column but does not result in an open vertebral canal has been labeled occult spinal dysraphisms[101] and includes

- Lipomeningocele
- Intradural lipoma
- Split cord syndrome (diastematomyelia)
- Tight filum terminale
- Dermoid cyst or sinus
- Aberrant nerve roots
- Anterior sacral meningocele (when occurring in conjunction with sacral agenesis—Currarino syndrome)
- Cauda equina tumor

These lesions may exist with no obvious signs, but 78%–90% of the children manifest a cutaneous abnormality overlying the lower spine.[11,102] The abnormalities include a small dimple or skin tag or a tuft of hair, a dermal vascular malformation, asymmetry of the gluteal cleft, and/or a very noticeable subcutaneous lipoma (Figure 53.7). On careful inspection of the legs, one may note a high-arched foot or alterations in the configuration of the toes, with hammer or claw digits. Other signs include a discrepancy in muscle size and strength between the legs, with weakness at the ankle, and/or a gait abnormality, especially in older children, as a result of shortness of one leg.[103–105] Absent perineal sensation and back pain are not uncommon symptoms in older children or young adults.[104,106,107] LUT function is abnormal in 40% of affected individuals.[108] The child may experience difficulty with urinary control (especially during the pubertal growth spurt), urinary retention, recurrent UTI, and/or fecal soiling after an initial period of continence.

Findings

The majority of children evaluated in the newborn or early infancy period have a normal neurologic examination. Urodynamic testing, however, will reveal abnormal LUT function in about one-third of <18-month-old babies (Figure 53.8).[10,109] These studies may provide the only evidence for a neurologic injury involving the lower spinal cord.[109–111] When present, the most likely abnormality is an upper motor neuron (UMN) lesion characterized by DO and/or hyperactive sacral reflexes, with mild forms of DSD being noted less often. LMN signs with denervation potentials in the sphincter, or detrusor underactivity, occur in only 10% of very young children.

In contrast, practically all individuals in the group of >3 years of age who have not been operated on or have been belatedly diagnosed as having an occult dysraphism will have either a UMN and/or LMN lesion on urodynamic testing (92%) (Figure 53.8), or neurologic signs of lower extremity dysfunction.[106,109,111–113] There does not seem to be preponderance for one type of lesion over another (UMN vs. LMN), and often the child manifests signs of both.[112,114]

Pathogenesis

The neurologic findings of occult dysraphism may be related to (1) compression on the cauda equina or sacral nerve roots by an expanding lipoma or lipomeningocele,[115] or (2) tension on the cord from tethering secondary to differential growth rates between the bony and neural elements.[103] The stretching that occurs when there is forcible flexion and/or extension of the spinal cord leads to changes in oxidation–reduction of cytochrome oxidase, most notably in the lumbosacral spinal neurons.[116] *Under normal circumstances, the conus medullaris terminates just below the L-2 vertebra at birth and recedes upwards to T-12 by adulthood.*[117] When the cord does not "rise" secondary to one of these lesions, ischemic injury may ensue.[116,118] Correction of the lesion in infancy has resulted in not only stabilization but also improvement in the neurologic picture in some instances (Figure 53.9). Sixty percent of the babies with abnormal urodynamic findings preoperatively reverted to normal postoperatively, with improvement noted in 30%, whereas 10% worsened with time. In the older child, there is a less dramatic change following surgery, with only 27% becoming normal, 27% improving,

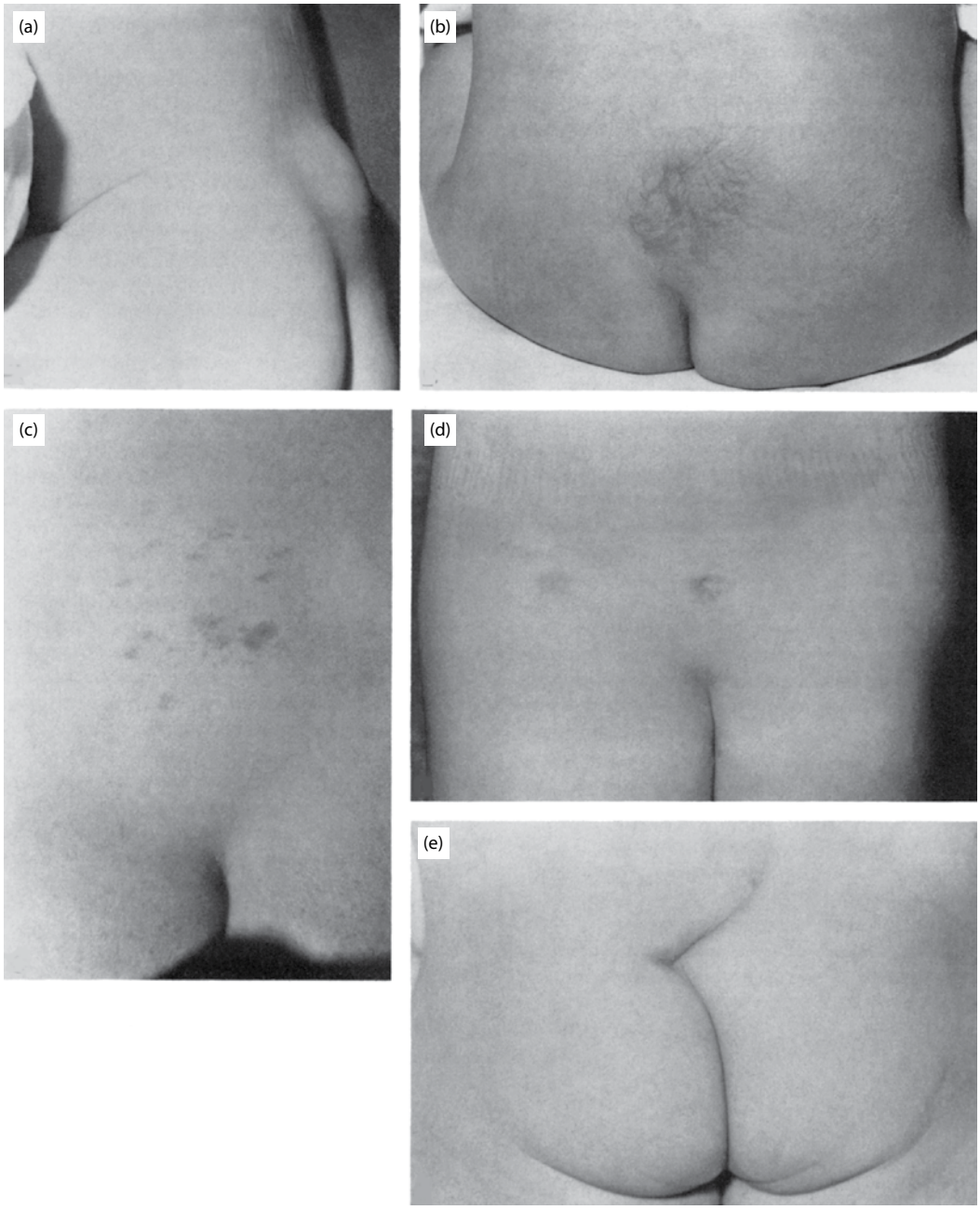

FIGURE 53.7 Cutaneous lesions occur in 90% of children with various occult dysraphic states. These lesions may vary from a small lipomeningocele (a) to a hair patch (b), a dermal vascular malformation (c), a dimple (d), or an abnormal gluteal cleft (e).

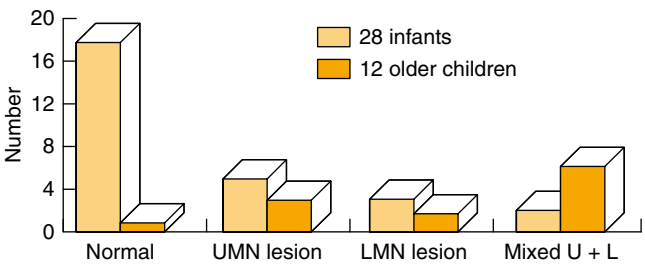

FIGURE 53.8 Most newborns with a covered spinal dysraphism have normal LUT function, whereas older children tend to have both UMN and LMN lesions. U + L = upper and lower motor neurons.

27% stabilizing, and 19% worsening (Figure 53.9).[109] The response to surgical untethering seems to be age related, with infants being more likely to improve than older children.[111] Older individuals with DO tend to improve, whereas those with an underactive bladder do not.[112,114,119] Finally, fewer than 5% of the children operated on in early childhood develop secondary tethering when observed for several years, suggesting that early surgery has both a beneficial and sustaining effect.

From these observations, it appears that urodynamic testing is the best method to determine whether an occult spinal dysraphism is affecting lower spinal cord function.[109,120] Some investigators have shown that posterior tibial somatosensory evoked potentials are an even more

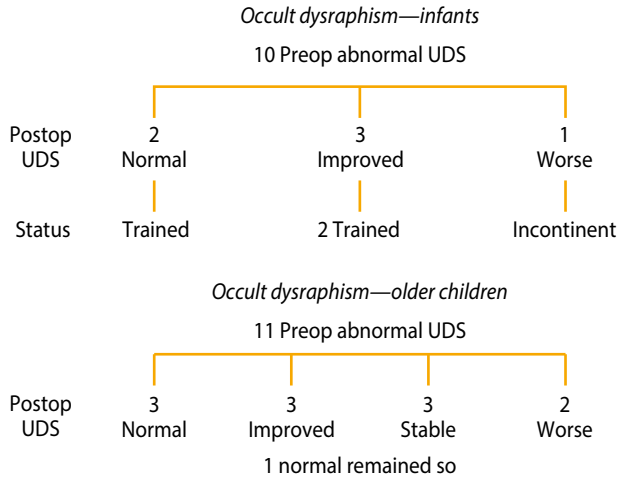

FIGURE 53.9 Potential for recoverable function is greatest in infants (6/10 [60%]) and less in older children (3/11 [27%]). The risk of damage to neural tissue at the time of exploration to those with normal function is small (2/19 [11%], not shown). UDS = urodynamic study.

sensitive indicator of tethering and should be an integral part of the urodynamic evaluation.[121] The implication is that early detection and intervention are both associated with reversibility of the lesion that is lost in the older child[115,118,122,123] and a degree of protection from subsequent tethering, which seems to be a frequent occurrence when the lesion is not treated expeditiously in infancy.[124]

Recommendations

Both MRI and urodynamics should be conducted in everyone who has a questionable skin or bony abnormality of the lower spine.[125–129] It is the most reliable way to detect a neurologic deficit involving the lumbosacral spinal cord initially, following surgical correction and as a means of predicting and identifying subsequent tethering, which can occur in 10%–20% of children.[129]

If the child is younger than 4 months of age, ultrasonography may be useful to image the spinal canal before the vertebral bones have ossified.[130,131] At this age, there is good correlation between the ultrasound and MRI findings, but the latter gives better definition of the lesion affecting the spinal cord.[132] Thus, ultrasound provides a screening modality, but spinal MRI is definitive.

In the past, removal of the superficial skin lesions without dissecting further into the spinal canal to remove or repair the entire abnormality was the standard treatment. Today, most neurosurgeons advocate laminectomy and removal of the intraspinal process as completely as possible without injuring the nerve roots or cord as soon as feasible after the diagnosis is made in order to release the tethering and prevent further injury that might ensue with subsequent growth.[105,107,110–112,123]

Sacral Agenesis

Sacral agenesis has been defined as the absence of part or all of two or more lower vertebral bodies. Although the etiology of this condition is still uncertain, a number of factors have been implicated. Teratogenic factors may play a role; *insulin-dependent mothers have a 1% chance of giving birth to an affected child. Conversely, 16% of children with sacral agenesis have a diabetic mother.*[133,134] Maternal drug exposure to minoxidil has also been reported as a cause.[135] In cases of sacral agenesis associated with the Currarino syndrome (presacral mass, sacral agenesis, and anorectal malformation), deletions have been identified in chromosome 7q, resulting in mutations of HLXB9, which appears to be responsible for neural plate infolding.[136,137] Thus, sacral agenesis may represent one point on a spectrum of abnormalities that encompasses sacral meningoceles and anorectal malformations.[138]

Diagnosis

The diagnosis is often delayed until failed attempts at toilet training bring the child to medical attention.[134] Sensation, including perianal dermatomes, is usually intact, and lower extremity motor function is normal.[139–141] Sacral vertebral bony ossification begins at 15 weeks, so it is possible to detect the abnormality after 18 weeks of gestation by prenatal ultrasonography and confirm by fetal MRI.[142] The lesion is often overlooked because these children have normal sensation and little or no orthopedic deformity involving the lower extremities (although high-arched feet and/or claw or hammer toes may be present). The only clue, requiring a high index of suspicion, is flattened buttocks and a low or short gluteal cleft (Figure 53.10).[143] Palpation of the coccyx will detect the absent vertebrae.[144] *The diagnosis is confirmed with a lateral film of the lower spine, because this area is often obscured by overlying*

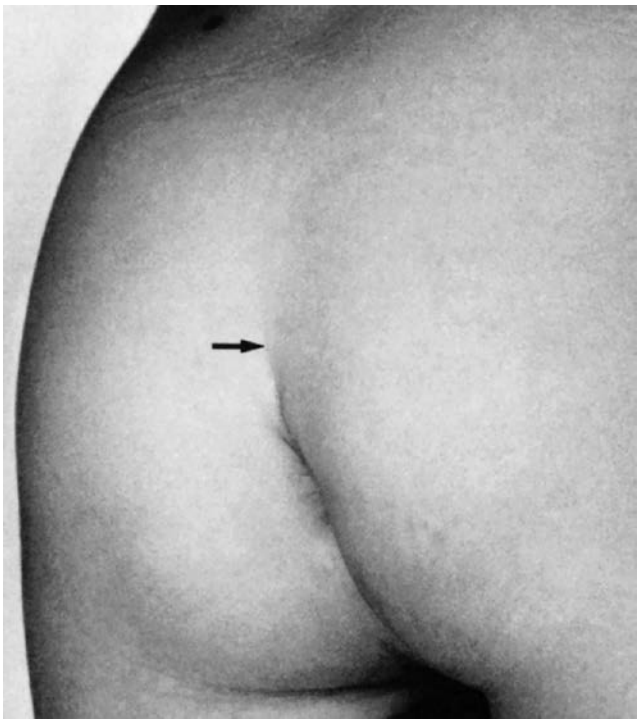

FIGURE 53.10 Characteristically, the gluteal crease is short and seen only inferiorly (below arrow) as a result of the flattened buttocks in sacral agenesis.

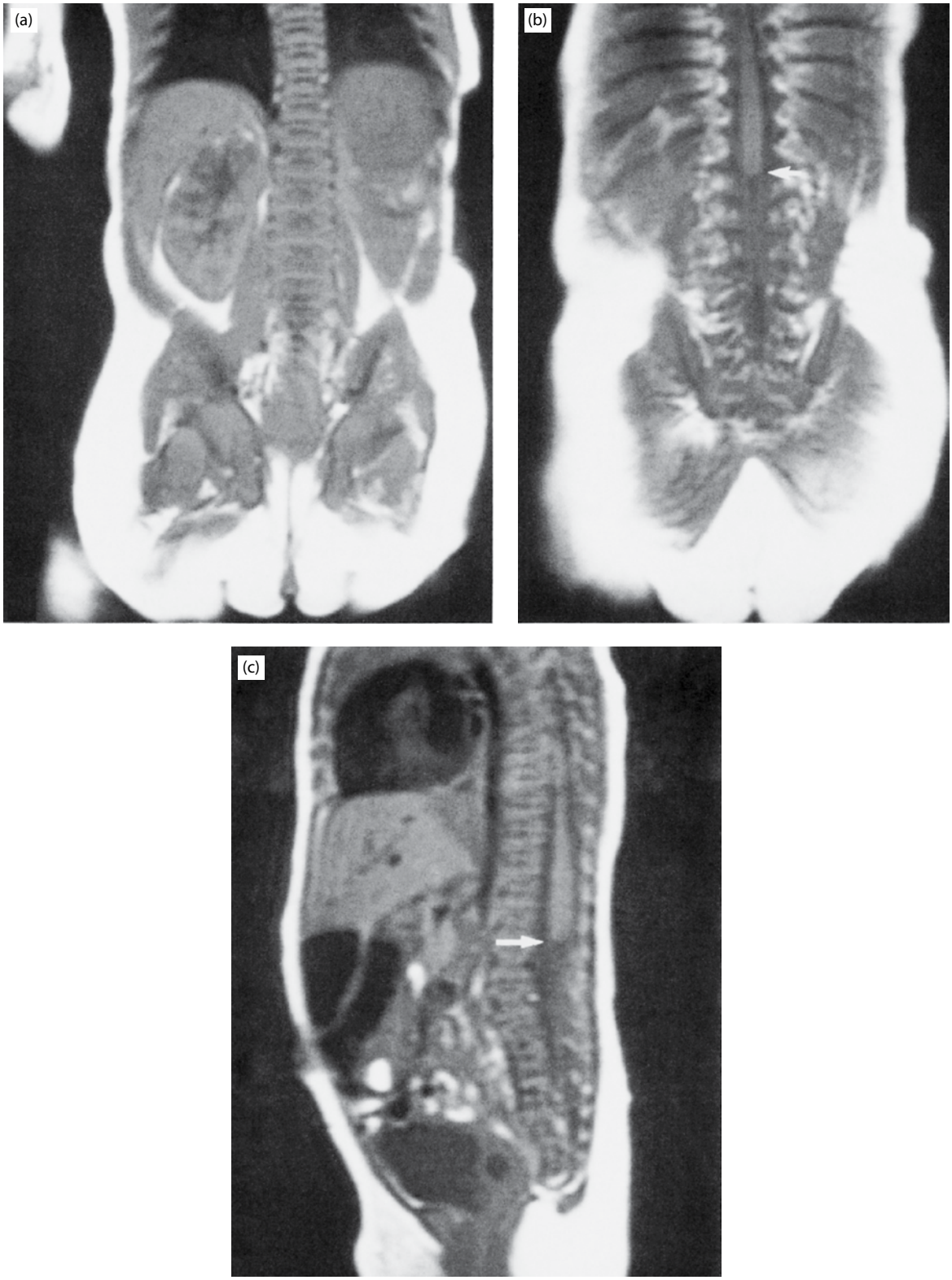

FIGURE 53.11 Coronal (a, left and right) and sagittal (b) magnetic resonance images in a 6-month-old girl with sacral agenesis at S-1 reveal a squared lower limit of the cord adjacent to T-12 (arrow). Note a solitary right kidney (a, left).

gas on an anteroposterior projection.[134,144] MRI has been used to visualize the spinal cord in these cases; a sharp cutoff of the conus opposite the T-12 vertebra seems to be a consistent finding (Figure 53.11).[145]

Urodynamic Findings

Urinary incontinence and recurrent UTIs are common in patients with sacral agenesis, occurring in 85% and 74% of patients, respectively.[12] When urodynamic studies are

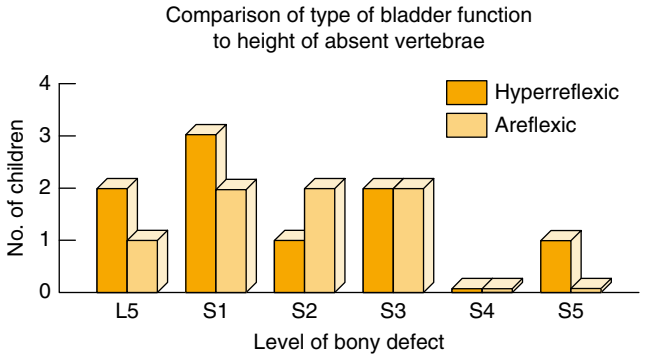

FIGURE 53.12 Bladder contractility is unrelated to the number of absent vertebrae. (Adapted from Bauer SB. Early evaluation and management of children with spina bifida. In King LR, ed., *Urologic Surgery in Neonates & Young Infants*. Philadelphia: Saunders, 1988, 252.)

undertaken, almost an equal number will manifest a UMN or LMN lesion (35% vs. 40%, respectively), whereas 25% have no signs of denervation at all.[134] The lesion is characterized by DO, exaggerated sacral reflexes, the absence of voluntary control over sphincter function, DSD, and no electromyographic evidence of denervation potentials in the urethral sphincter.[134,139,141,144] VUR occurs almost exclusively in children with poor compliance with or without dyssynergy.[146] An LMN lesion is noted when detrusor underactivity and partial or complete denervation of the EUS with diminished or absent sacral reflexes are seen. The bladder is usually small and smooth walled, with an open bladder neck.[146] The number of affected vertebrae does not correlate with the type of motor neuron lesion present (Figure 53.12). The lesion rarely shows signs of progression. It is unclear whether spinal cord detethering improves urodynamic parameters postoperatively.[147]

Recommendations

Management depends on the specific type of neurourologic dysfunction seen on urodynamics, as detailed previously in this chapter. Anorectal manometry has identified abnormalities in the internal anal sphincter and in voluntary anal sphincter squeeze pressure, leading to weakness of the muscle and fecal incontinence.[148] It is important to identify these individuals as early as possible so that they can be rendered continent at an appropriate age, avoiding the social stigmata of fecal and/or urinary incontinence.

Associated Conditions

Imperforate Anus

Imperforate anus is a condition that occurs alone or as part of a constellation of anomalies that has been called the VATER or VACTERL syndrome.[134] This mnemonic stands for the organs that possibly can be affected (V = vertebral, A = anal, C = cardiac, TE = tracheoesophageal fistula, R = renal, L = limb). This may be part of a spectrum of hindgut abnormalities that includes sacral agenesis and Currarino syndrome (discussed above).[29,147] Urinary incontinence is relatively rare unless there is coexisting spinal cord pathology or the pelvic floor muscles and/or nerves have been injured during the imperforate anus repair.[149] An abdominal plain film and an ultrasound of the spine and kidneys are obtained in the neonatal period regardless of the level of the rectal atresia, once the child has either stabilized or has had a colostomy performed.[150–152] Vertebral bony anomalies often signify an underlying spinal cord abnormality. Any hint of an abnormality on these studies or the presence of a lower midline skin lesion overlying the spine warrants an MRI to evaluate for a potentially pathologic intraspinal process.[153] If radiographic images demonstrate an abnormality, urodynamic studies are recommended. Urodynamics are also indicated before repair in the child with high imperforate anus who has undergone an initial colostomy. Abnormal findings may provide a reason to explore and treat any intraspinal abnormality in order to improve the chances of fecal and urinary continence. In addition, they furnish a baseline for future comparison, particularly for those children needing extensive surgery for their imperforate anus.

EMG studies of the perianal musculature help to define the optimal location for the future anus. Before the Peña operation (a posterior midline approach) was developed to correct a high imperforate anus, rectal incontinence was thought to be due to an injury involving the pelvic nerves that innervate the levator ani muscles.[154–156] Because the Peña approach is confined to the midline area, this procedure has reduced the chance of traumatizing nerve fibers that course laterally and around the bony pelvis from the spine to the urethral and rectal sphincter muscles. Despite careful dissection techniques, 37% of patients still have long-term problems with fecal incontinence.[157] Urodynamic and perianal EMG studies are repeated after imperforate anus repair, if fecal and/or urinary continence has not been achieved by a reasonable age or if urinary incontinence develops secondarily.

Thirty to seventy percent of affected children have a spinal abnormality even though they may not have any associated anomalies.[158,159] The incidence of NBD is related to the presence (64%) or absence (31.5%) of a sacral bony defect. Similarly, the level of the anal atresia determines the incidence of NBD, with supralevator atresia having a higher risk (70%) than infralevator (35%) lesions.[152] Boemers et al.[160] found impaired LUT function in 24% of 90 children; all but one had a sacral bony abnormality, suggesting an even closer association of dysfunction with abnormal bony spinal development. The abnormality may range from tethering of the spinal cord secondary to an intraspinal dysraphism producing a UMN type of dysfunction, to an atrophic abnormality of the conus medullaris, which leads to a partial or complete LMN lesion involving the LUT.[161] In these circumstances, urinary and fecal incontinence might be the child's only complaints. Because lower extremity function may be totally normal, an examination of the legs alone can be misleading.[159]

CENTRAL NERVOUS SYSTEM INSULTS

Cerebral Palsy

Etiology

Cerebral palsy (CP) is a nonprogressive injury to the brain in the perinatal period that produces a neuromuscular

disability or a specific symptom complex of cerebral dysfunction. In 2006, the prevalence of CP in the United States was estimated at 3.3 per 1000 children.[162] It is usually due to a perinatal infection or period of anoxia (or hypoxia) that affects the CNS.[163,164] CP most commonly appears in babies who were premature and of low birth weight, but it may be seen following a seizure, infection, or intracranial hemorrhage in the neonatal period.

Diagnosis

Affected children have delayed gross motor development, abnormal fine motor performance, altered muscle tone, abnormal stress gait, and exaggerated deep tendon reflexes. The findings can vary substantially from being very obvious to exquisitely subtle. Among the more overtly affected individuals, spastic diplegia is the most common of the five types of dysfunction that characterize the disease, accounting for nearly two-thirds of the cases.

Findings

Most children with CP develop total urinary control. Incontinence is a feature in some, but the exact incidence has never been truly determined.[165,166] Bladder dysfunction appears to be more common in children with a greater degree of motor dysfunction.[167] A 2001 survey of more than 600 families with an affected child aged 4–18 years demonstrated that 23.5% had persistent urinary incontinence.[168] When urinary continence was achieved, its development was delayed when compared with that of normal children of similar age. With further analysis of the data, 80% of children with spastic diplegia, 54% with tetraplegia, and 38% with low intellectual capacity attained continence. The presence of incontinence was related in part to the extent of the physical impairment because this prevents the individuals from reaching the toilet expeditiously. If the children are cognitively delayed, they either do not recognize the need to void or do not relate this fact to caregivers early enough to be toileted.[168] Some children have such a severe degree of cognitive delay that toilet training is not feasible, but the majority are able to attain social control, albeit at a later than expected age. Daytime continence is attained first, and nocturnal continence ensues within the subsequent year.[168] Therefore, urodynamic evaluation is reserved for children who appear trainable and not hampered by their physical impairment, but who have not achieved continence by later childhood or early puberty.

Several studies have examined urodynamic parameters in children with CP.[166,169] One series found only 29% of patients with CP and urinary symptoms had normal urodynamic findings, with reduced bladder capacity seen in 54% and DO seen in 35%.[170] The most typical pattern includes UMN dysfunction with DO and/or DSD. However, some patients also exhibit an LMN lesion, most of whom experienced an episode of cyanosis in the perinatal period. In a meta-analysis of all published reports of urodynamic findings in children with CP, DO was seen in 80%, DSD in 5%, and normal function in only 12%.[166,169,171] These reports suggest that urodynamic studies can be revealing in all children with CP,[169] and are especially useful if frequent toileting or initial anticholinergic treatment fails to improve incontinence, the child develops UTI, or hydronephrosis develops.

Recommendations

Therapeutic goals include treating DO with anticholinergics, but residual urine volume must be monitored closely. CIC may be required for those who cannot empty. Selective dorsal sacral rhizotomy has helped with spasticity and incontinence, with <5% developing incontinence if careful mapping delineates the dorsal sacral nerve roots.[172,173]

Traumatic Injuries to the Spine

Traumatic spinal cord injury (SCI) is a rare entity in children; the incidence in Sweden is 2.6 cases per million children per year,[174] and SCI accounts for only 1.3% of pediatric traumas in the United States.[175] Motor vehicle accidents are the most common mechanism overall.[174,176–178] Within specific age groups, infants are more prone to an injury from a motor vehicle accident (71%), toddlers and children secondary to a fall (48% and 34%, respectively), and adolescents due to a sporting event (29%).[177] SCI has also occurred iatrogenically following spinal and vascular surgery.[176,179] Newborns are particularly prone to hyperextension injuries during a high forceps delivery.[180,181]

The LUT dysfunction due to SCI is usually associated with loss of sensation and paralysis of the lower limbs. Radiologic investigation of the spine may not reveal any bony abnormality, even though momentary subluxation of osseous structures due to the high elasticity of vertebral ligaments can result in a neurologic injury.[182] This has been labeled spinal cord injury without radiologic abnormality (SCIWORA), and it can account for up to 38% of pediatric SCIs.[178] Imaging will show swelling of the cord below the level of the lesion, central disk herniation, spinal stenosis, or contusion.[180,181,183] Often, what appears initially as a permanent lesion turns out instead to be a transient phenomenon. Although sensation and motor function in the lower extremities may be restored relatively soon, the dysfunction involving the bladder and rectum may persist for considerably longer.

If urinary retention occurs immediately following the injury, an indwelling Foley catheter is inserted and left in place for as short a time as possible until CIC can be started safely.[184,185] When the child resumes voiding, CIC is used to measure residual urine; residuals of <25 mL are considered safe enough to allow for weaning and cessation of CIC as long as voiding pressures are not excessive (i.e., >60–70 cm H_2O).[185] If there is no improvement in urinary tract function after 4–6 weeks, urodynamics are conducted to determine whether the condition is the result of spinal shock, nerve root injury, or SCI. Sustained detrusor underactivity is not uncommon under these circumstances.[186] An EMG recording of the sphincter often reveals normal motor units without fibrillation potentials, but absent sacral reflexes, and a nonrelaxing sphincter with bladder filling indicates transient spinal shock.[186] The outcome from this latter condition is guarded but favorable; most cases resolve completely as edema of the cord in response to the injury subsides, leaving no permanent damage.[186,187]

Most permanent traumatic SCIs involve the upper thoracic or cervical spinal cord, but some affect the cauda equina region. Sacral SCI usually produces an LMN deficit of the striated sphincter that leads to low-pressure bladder emptying with little risk of upper urinary tract deterioration. However, it often necessitates medical and/or surgical therapy to achieve continence. Conversely, upper SCIs can produce a lesion associated with DO and DSD. The potential danger from this outflow obstruction is obvious.[188] Substantial residual urine volumes, poor compliance, high voiding pressure, reflux, UTIs, and their sequelae are the leading cause of long-term morbidity and mortality in SCI patients. Urodynamics will identify those patients at risk.[185] *Even if the child is continent and voiding to completion or requires CIC to empty, it is imperative to perform urodynamics to assess for risk to the upper urinary tract.*[189] *Early identification and proper management may prevent the signs and effects of BOO before they become apparent on x-ray examination of the urinary tract.*[190–192]

FUNCTIONAL VOIDING DISORDERS

Children without obvious neurologic disease may have a voiding abnormality on a functional or maturational basis. Most children gain urinary control before 5 years of age. Persistent day and night incontinence without a prolonged period of dryness or the recurrence of nocturnal wetting lasting into puberty is an indication for urodynamic evaluation in neurologically normal children. Although many children have normal urodynamic findings, greater than 30% of patients may have a dysfunctional voiding state.[193]

ICCS Classification of LUT Symptoms

In order to understand these disorders, it is helpful to recall the ICCS classification of various LUT symptoms and the specifics regarding urinary incontinence in children:[15]

1. Storage symptoms
   a. Increased or decreased voiding frequency
   b. Incontinence
   c. Urgency
   d. Nocturia
2. Voiding symptoms
   a. Hesitancy
   b. Straining
   c. Weak stream
   d. Intermittency
3. Other symptoms
   a. Holding
   b. Feeling of incomplete emptying
   c. Postmicturition dribble
   d. Genital or LUT pain

Urinary incontinence is defined by the ICCS as the uncontrolled leakage of urine; it can be continuous or intermittent, occurring during the daytime or nighttime. Continuous incontinence means leakage of urine all the time that denotes the probability of an ectopic ureter. It is abnormal at any age because even infants have a degree of cortical control over bladder emptying, void at reasonably spaced intervals, and stay dry between urinations. Daytime (diurnal) incontinence may be on an urgent or sudden basis, associated with stress activity, such as coughing or running, or occur just after voiding (only in girls, resulting from the vaginal trapping of urine during voiding that drips out afterwards). Nocturnal incontinence (enuresis) means the leakage of urine while asleep at an age when urinary control is expected. It is difficult, however, to say when this should occur. Studies of large groups of children have provided some guidelines for expectations, but there are no absolute milestones for the individual child.[194,195] Girls tend to become trained before boys, and daytime continence is achieved before nighttime control. It is rare to achieve control before 18 months of age.[196] Thereafter, urinary control is gained by approximately 20% of children for each year of life up to 4.5 years. By the age of 10, about 5% of children still have some nocturnal wetting, diminishing to 2% after puberty.[197] Recently, evidence has come to light that there may be a genetic basis for the development of urinary control.[198–200]

Recommended Evaluation

The evaluation of a neurologically normal-appearing child with incontinence and/or other evidence of voiding dysfunction includes

- History and physical examination
- Voiding diary
- Radiologic evaluation
  - Renal and bladder ultrasound
  - Abdominal x-ray
  - ± VCUG
- Noninvasive urodynamic testing
  - Uroflowmetry
  - Flow EMG
- ± Invasive urodynamic testing

The assessment of the child with incontinence and/or other LUT symptoms begins with a comprehensive history. This includes detailing any family history of enuresis; the mother's pregnancy, including the presence of maternal insulin-dependent diabetes; the stage of gestation at the time of delivery; Apgar scores, difficulties occurring perinatally or early postnatally; and developmental milestones, including school performance. History of fine and gross motor incoordination, previous continence, social setting and sibling interaction, parental expectations, and characterization of the wetting episodes are also important. A voiding diary provides a representation of the child's typical patterns of urination and leakage, and creates a baseline for future comparison. One group of clinicians has developed a comprehensive questionnaire that accurately identifies and quantifies children with abnormal voiding patterns that has been used successfully in determining responses to therapy.[201]

If there is a suspicion of an ectopic ureter in a girl (normal voiding, but constant dampness), then renal and bladder ultrasonography is performed. Although not yet standard of care, bladder ultrasound has also been helpful in determining bladder wall thickness in

this population, which may be predictive of poor urodynamic parameters, such as high detrusor pressure.[202] In the future, this may be used as a basic screening study to triage patients to invasive urodynamic testing. Abdominal radiographs allow visualization of the colonic stool load, as well as the sacrum. Boys who have a question of bladder outflow obstruction (urgency or urge incontinence with enuresis beyond the age of 5 years despite basic urotherapy maneuvers) are evaluated by voiding cystography.

Noninvasive urodynamic testing (uroflowmetry or flow EMG) can help to differentiate the patient's specific type of voiding dysfunction through examination of the flow rate and pattern.

The indications for performing invasive urodynamic studies for patients with functional voiding disorders are as follows:

- Any suspicion of a neurologic condition
- Diurnal incontinence with no associated pathology
- Fecal and urinary incontinence at any age
- Persistent voiding difficulties long after a UTI has been treated
- Recurrent UTI despite continuous antibiotics
- Bladder trabeculation and/or "sphincter spasm" on VCUG (Figure 53.13)
- Persistent LUT symptoms while on anticholinergics
- Recurrence of symptoms after the cessation of successful medical therapy

FIGURE 53.13 This 10-year-old girl with recurrent UTIs has spasm of the sphincter during voiding, with narrowing in the distal urethra, demonstrated on this voiding cystourethrogram (arrow). Note the grade II/V right-sided reflux.

When urodynamic studies are performed on a group of children who have these findings without an obvious systemic neurologic disorder, a spectrum of abnormalities emerge that can be classified in accordance with the ICCS classification of LUT symptoms:[15]

1. Storage disorders
   a. Overactive bladder
   b. Urge incontinence
   c. Voiding postponement
   d. Underactive bladder
2. Voiding disorders
   a. Dysfunctional voiding
      i. Psychological nonneuropathic bladder

General Approach to Treatment

Urotherapy via a comprehensive, multimodal approach is the mainstay for functional voiding disorders. This strategy is effective for both DO and functional causes of incomplete emptying, such as incomplete relaxation of the pelvic floor muscles. The urotherapy approach focuses on behavioral management, and includes timed voiding, regulation of fluid intake, elimination of caffeine from the diet, instructions on proper toileting posture, biofeedback, and treatment of constipation (if necessary).[203–205] *Urotherapy benefits up to 90% of children with LUT symptoms due to voiding dysfunction, and results appear to be durable both in the short term*[205] *and into adulthood.*[204] Recently, biofeedback training using computer technology has been employed successfully to achieve continence and to reduce the need for medication in children refractory to anticholinergic medication.[206–209] In some centers, biofeedback therapy is employed initially. Pharmacologic treatment, as detailed in the beginning of the chapter, serves as an important adjunct for children with voiding dysfunction, but it is not generally the primary treatment strategy.

Overactive Bladder, Voiding Postponement, and Urge Incontinence

Children with long-standing symptoms of daytime frequency, urgency, or sudden incontinence and squatting, in addition to nocturia and/or enuresis, may have DO. Vincent's curtsy, a characteristic posturing by these children in an attempt to prevent leakage, is a commonly described behavior pattern.[210,211] When micturition is postponed, many of these children also manifest urge incontinence. One or more of the child's parents or siblings often have a history of delayed control over micturition and/or LUT symptoms into later childhood or puberty. These affected family members may compensate for their own abnormality by displaying continued daytime frequency and/or nocturia. Although the child's physical examination may be normal, hyperactive deep tendon reflexes in the lower and/or upper extremities, tight heel cords, ankle clonus, posturing with a stress gait, or difficulty with tandem walking, and mirror movements (similar motion in the contralateral hand when the individual is asked rapidly to pronate and supinate one hand) may be evident. Left-handedness, left-footedness, or left-eyedness in a family in which all other members

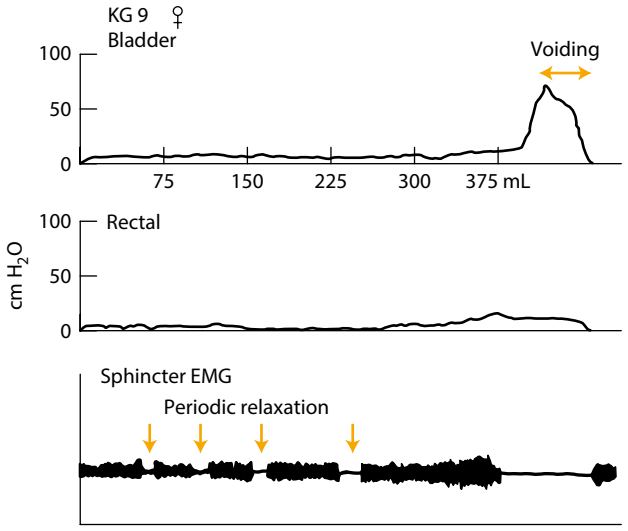

FIGURE 53.14 Some children only manifest periodic relaxation of the sphincter without a rise in detrusor pressure as an early phase of a hyperreflexic bladder producing urgency and incontinence.

are right-handed may signify crossed dominance from a previously unrecognized perinatal insult. Attention deficit disorders, poor writing ability and/or incoordination, and learning difficulties are also more commonly encountered in these children.[212,213] Carefully questioning parents about perinatal events or reviewing birth history records may uncover an insult that affected the CNS and caused these findings. The dysfunctional voiding symptom score devised by the group in Toronto has been successfully used to identify and treat children with subtle effects of such insults.[201]

Radiologic evaluation usually reveals no abnormality other than a mildly trabeculated or thick-walled bladder. Noninvasive urodynamics reveal a tower uroflow pattern with complete emptying and a total quieting of the sphincter on EMG measurements. Invasive urodynamics demonstrate premature bladder contractions during filling, which the child may or may not sense and/or abolish by increasing the activity of the EUS.[214,215] Alternatively, periodic relaxation of the sphincter, the initial phase of an overactive contraction that leads to a sense of urgency or to an episode of leaking, may be the only clue to an overactive bladder (Figure 53.14). Urethral instability can also occur along with DO, resulting in incontinence (Figure 53.15). During filling, capacity may be reached sooner than expected, at which time a normal detrusor contraction occurs with a sustained relaxation of the sphincter, resulting in complete emptying. Some children will not be able to suppress this contraction even though the bladder has not been filled to its intended capacity. Sometimes, DO may only be elicited following a cough or strain, or when the child assumes a change in posture.[211] The overactivity is thought to be responsible for the symptoms.[216]

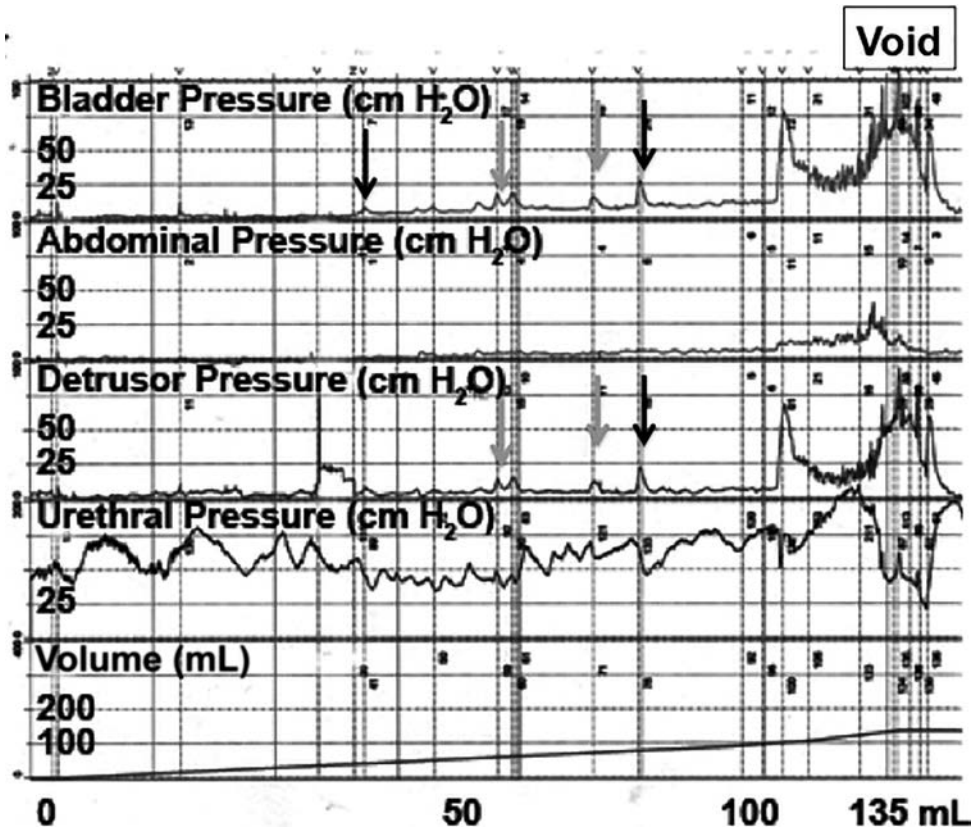

FIGURE 53.15 Urodynamic tracing demonstrating urethral instability. Some periods of overactivity are associated with drops in urethral pressure (black arrows) and some with an increase in urethral resistance (gray arrows). Detrusor instability during periods of low urethral resistance results in urge incontinence.

These findings may be the result of a cerebral insult, however mild, in the neonatal or prenatal period, but they are linked more commonly to delayed maturation of the reticulospinal pathways and the inhibitory centers in the midbrain and cerebral cortex. Thus, total control over vesicourethral function may be lacking.[196,197,217] Several investigators have found a similar urodynamic picture in a significant number of adults with nocturnal enuresis and/or daytime symptoms.[218] Parents who exhibit the same behavior pattern as their children may have a genetically determined delayed rate of CNS maturation.[199] A recent functional MRI study of adult patients with urge incontinence found that increasing activation of specific cortical regions (dorsal anterior cingulate gyrus, insula, and parietal lobe) occurs with increasing severity of incontinence;[219] the ability to target individual regions of the brain may provide greater understanding of functional voiding disorders and new targets for therapy in the future.

Children with profound constipation can also develop DO that leads to urinary incontinence.[220] The etiology of this condition is unclear, but treatment of the bowel distention has resulted in a dramatic improvement in the bladder dysfunction.[221]

Sometimes, repeated UTI may produce an identical urodynamic picture. DO occurs as a result of the inflammatory response in the bladder wall that irritates the receptors located in the submucosa and/or detrusor muscle layers.[222] Therefore, these children should be evaluated for infection. It has been postulated that DO may lead to inappropriate voiding. The child realizes what is happening, and tightens the sphincter to reverse this process, which shuts the distal urethra first and the bladder neck second, causing the "milk-back" phenomenon and the potential for UTI, as presented in the previous discussion, to occur.[222,223]

If biofeedback therapy and continuous antibiotics (if recurrent UTI is present)[214,224,225] fail to nullify the symptoms, anticholinergics alone or in combination with other therapies have been used successfully to manage this condition.[211] Oxybutynin has been highly successful,[226] with tolterodine somewhat less so, primarily due to underdosing, but the latter is better tolerated than the former and constipation is less of an issue.[227]

Underactive Bladder

Most children urinate between four and seven times per day, and defecate daily or at least every other day. Some children, primarily girls, may void only twice a day, once in the morning (either at home or after they are in school) and again at night.[228] These children exhibited normal voiding patterns as infants, but after toilet training, they learned to withhold micturition for extended periods. As a result, a few develop a fear of strange bathrooms or mimic their mother's pattern of infrequent urination and defecation.[214]

The infrequent voiding and incomplete emptying produce an ever-increasing bladder capacity and a diminished stimulus to urinate.[223] The chronically distended bladder is at risk for UTI and/or overflow or stress incontinence. Sometimes, these signs are the first manifestations of the abnormal voiding pattern. When the child is carefully questioned, the aberrant micturition is easily detected. If a comprehensive history has not been taken and/or a voiding diary not completed, the problem is sometimes diagnosed following a VCUG or radionuclide cystography performed for an assessment of UTI. Findings include a larger than normal bladder capacity and/or a high residual volume on initial catheterization, but the bladder is usually smooth walled without reflux. When the child is questioned about voiding habits, this infrequent pattern of elimination is detected (Figure 53.16).[223]

Noninvasive uroflow reveals an interrupted stream with a large residual; flow EMG shows a quiet sphincter during the voids that occur by straining or Valsalva. The urinary flow rate may be intermittent, with sudden peaks coinciding with straining, or it may be normal but short-lived, secondary to an unsustained detrusor contraction.[223] Invasive urodynamics demonstrate a very large, highly compliant bladder with either normal, unsustained, or absent detrusor contractions (Figure 53.17a).[214] Sphincter EMG reveals normal motor unit potentials at rest and normal responses to sacral reflexes, bladder filling, and attempts at emptying. Unless strongly encouraged, the child will not completely empty the bladder during voiding (Figure 53.17b).[214] This picture is consistent with myogenic failure from chronic distention.[229]

Changing the child's voiding habits is the first approach to therapy.[230] A structured timed voiding schedule and encouraging children to empty each time they void are mandatory.[231] Behavioral therapy techniques to encourage compliance are also helpful. Constipation is often an accompaniment of this scenario; treating it aggressively with cathartics or stool softeners is imperative. Rarely, CIC may be necessary to allow the detrusor muscle to regain its contractility and ability to empty.[232] Antibiotics are needed when UTI is present and are continued until the voiding pattern improves and residual urine is minimal.

Dysfunctional Voiding

Dysfunctional voiding *is a specific term that denotes a type of voiding dysfunction characterized by discoordination of the detrusor and EUS that occurs only during the voiding phase of the micturition cycle.*[15,233] When children attempt to withhold urination because it is either painful or inappropriate to void, they may actually tighten or only partially or intermittently relax the EUS muscle during voiding. Children with this condition have LUT symptomatology, including frequency, urgency, urge incontinence, staccato or intermittent voiding, nocturia and/or enuresis, and dysuria.

Persistence of these symptoms with their associated abnormal voiding dynamics can lead to repeated infections.[234] An inflammatory reaction in the bladder wall may produce an irritability that affects the sensory threshold and increases the need to void sooner than anticipated. If the detrusor muscle is affected as well, the increased irritability may lead to DO and eventually to poor compliance.[224] The discoordination between the bladder

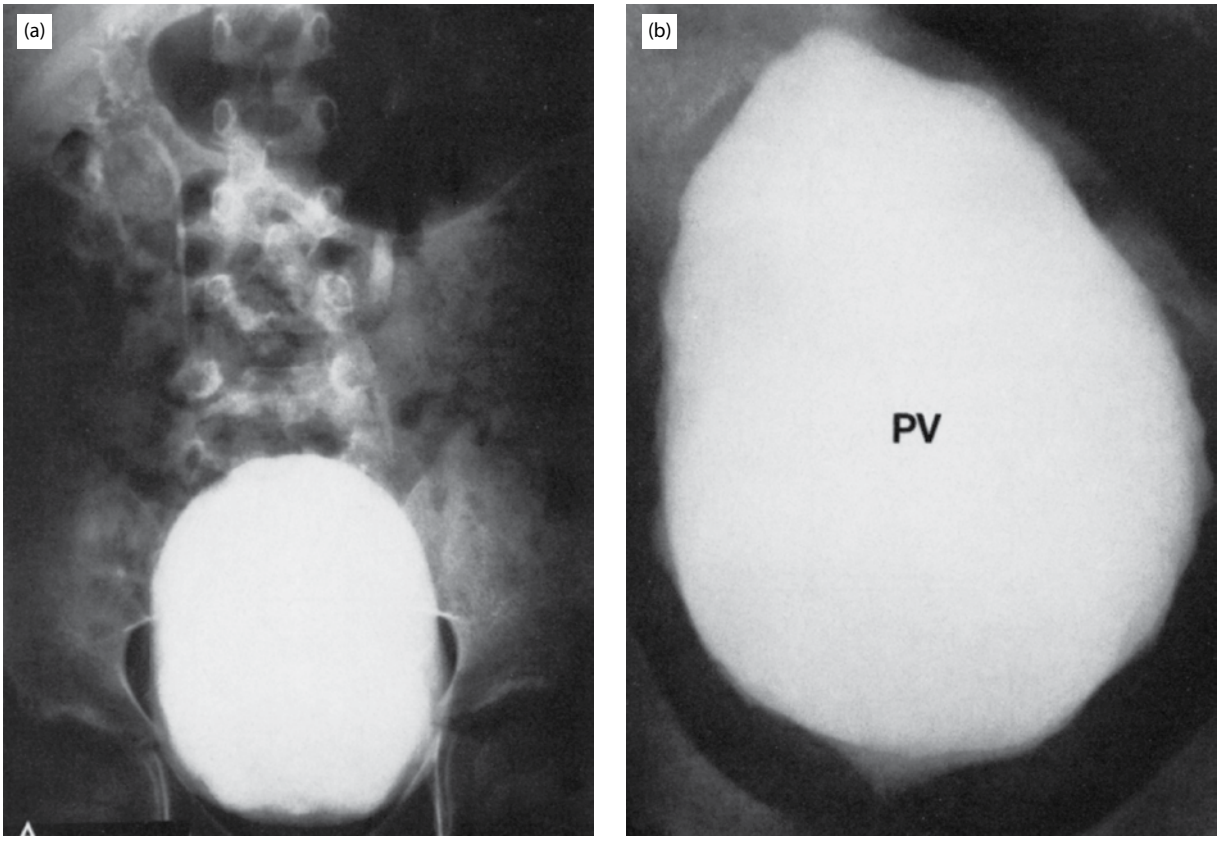

FIGURE 53.16 (a) Excretory urogram in a girl who urinates infrequently, demonstrating a large-capacity bladder with a normal upper urinary tract. (b) Her postvoiding (PV) residual is quite large.

and sphincter can also result in a functional BOO that disrupts the laminar flow pattern that normally exists (Figure 53.18).[234–236] This stop-and-start (staccato) voiding (Figure 53.19) is a prominent pattern of dysfunction in girls leading to recurrent infection,[237] because bacteria can be carried back up into the bladder from the meatus as a result of the milk-back phenomenon occurring within the urethra when urination is interrupted in this manner.[223] Theoretically, if unrecognized or left untreated in young girls, this may become the forerunner of interstitial cystitis seen in many adult females and may even be the precursor of prostatitis in males.

Radiologic investigation often reveals a normal upper urinary tract, but the bladder may be small and have varying degrees of trabeculation and/or a thickened wall.[214,238] During the voiding phase of cystourethrography, the posterior urethra may show signs of intermittent dilation at its upper end, with a uniform narrowing occurring toward the EUS region. In girls, this "spinning-top" deformity has raised the question of an obstructed meatus (Figure 53.13),[235,236] whereas in boys, it has often been mistaken for posterior urethral valves. This appearance is due to failure of complete relaxation of the EUS and persistence of a relative obstruction at the distal end of the posterior urethra as the child attempts to suppress voiding.[239]

Noninvasive uroflow reveals a staccato-type flow pattern with either complete emptying or a modest residual. During flow EMG, the sphincter may relax intermittently or even completely at first, but then contract in response to discomfort, preventing complete emptying (Figure 53.20).[234] Invasive urodynamic studies demonstrate a bladder of small capacity (when adjusted for age) and elevated detrusor pressure during filling (Figure 53.19).[214,236] At capacity, the child has an uncontrolled urge to void that may not be suppressed despite tightly contracting the EUS. The bladder contraction is usually sustained, with pressures reaching higher than normal values. Emptying may not always be complete despite these high pressures. The baseline sphincter EMG activity is normal at rest, but there may be complex repetitive discharges (pseudomyotonia)[240] or periodic relaxation of the muscle during filling, contributing to the sense of urgency or actual incontinent episodes.

Treatment goals include eliminating recurrent UTIs, minimizing environmental influences that predispose the individual to infection, and improving the child's voiding pattern and bathroom habits. Girls should learn to take showers instead of baths, or at least to bathe alone without other siblings; wipe from front to back; try to completely relax when they void so that a steady stream is produced; and take the time to empty completely each time they urinate.[234] Biofeedback training to teach these children to relax the sphincter when they void has been used, with 67%–80% of children benefiting.[206–208,231,241–243] In addition to antibiotics, antispasmodic and anticholinergic agents are administered for periods ranging from 6 to 9 months.

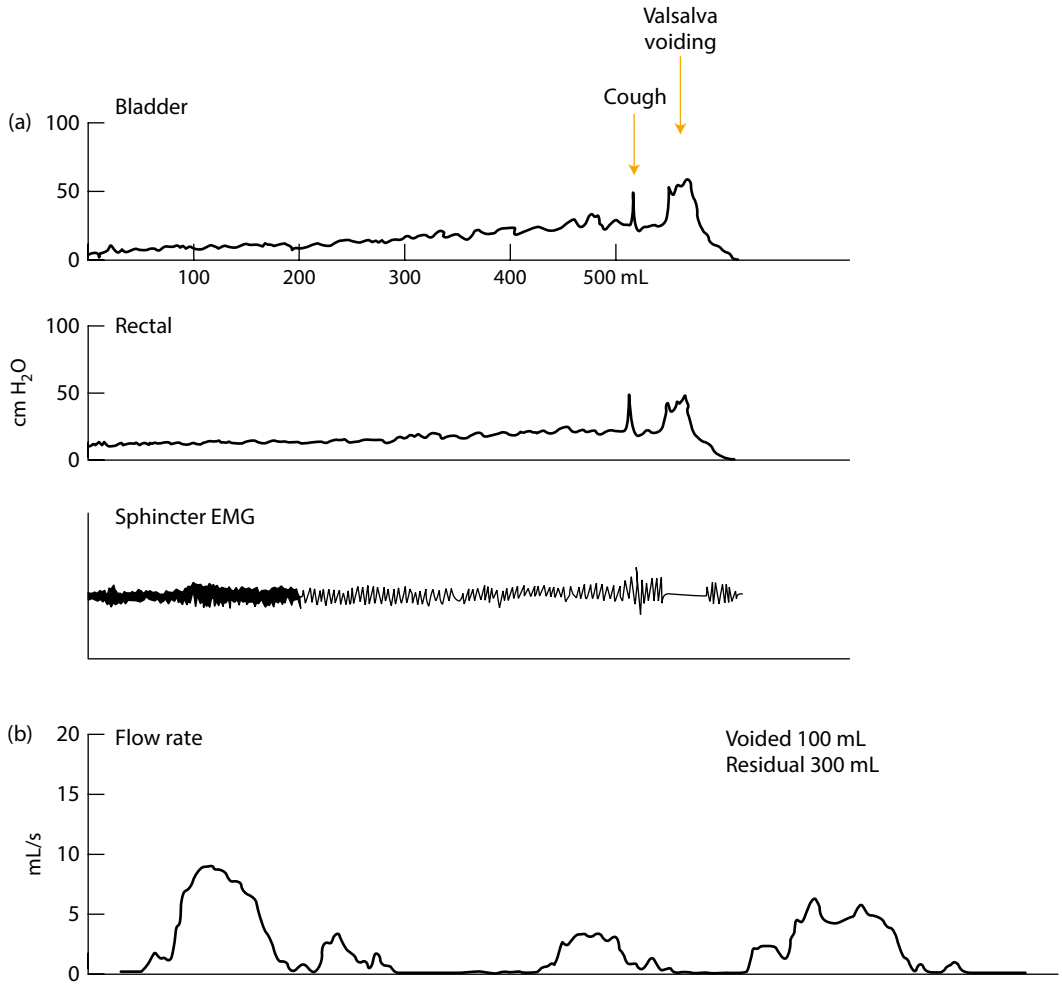

FIGURE 53.17 (a) Urodynamic evaluation reveals a very large-capacity, low-pressure bladder. The girl empties entirely by straining after relaxing the sphincter with no apparent detrusor contraction. (b) Her intermittent urinary flow rate is characteristic of this effort to empty and leads to a considerable volume of residual urine.

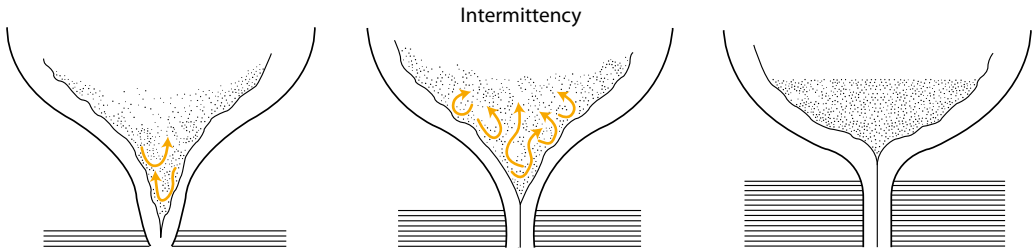

FIGURE 53.18 Nonlaminar flow secondary to periodic tightening and relaxation of the external sphincter leads to eddy current and the milk-back phenomenon, which can carry bacteria colonized at the urethral meatus up into the bladder and cause infection of the residual urine.

Psychological Nonneuropathic Bladder (Hinman Syndrome)

Hinman[244] described an apparent "syndrome" of severe voiding dysfunction that mimics NBD but is likely a learned disorder. At first, this syndrome was believed to be caused by an isolated neurologic lesion,[245–247] but now it is felt to be an acquired abnormality.[214,244,248,249] It is produced by an active contraction of the sphincter during voiding, creating a degree of outflow obstruction. Some investigators believe this phenomenon may be the result of persistence of the transitional phase of gaining control in which the child learns to prevent voiding by voluntarily contracting the EUS.[215,248] Others believe that this pattern results from the child's normal response to DO.[216] This behavior becomes habitual because the child has difficulty in distinguishing between involuntary and voluntary voiding; as a consequence, the inappropriate

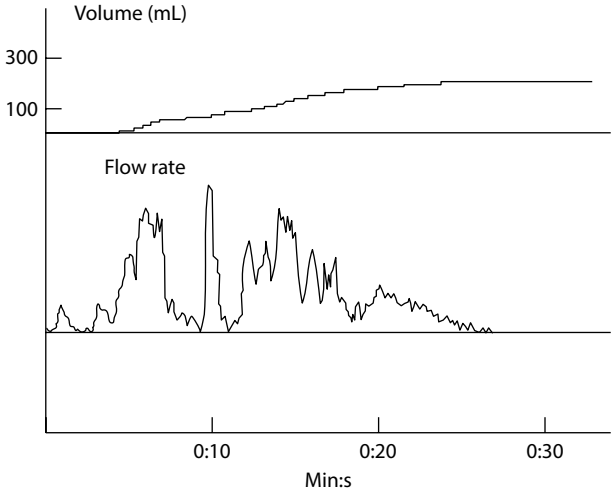

FIGURE 53.19 Staccato voiding is seen in this 8-year-old girl with recurrent infection.

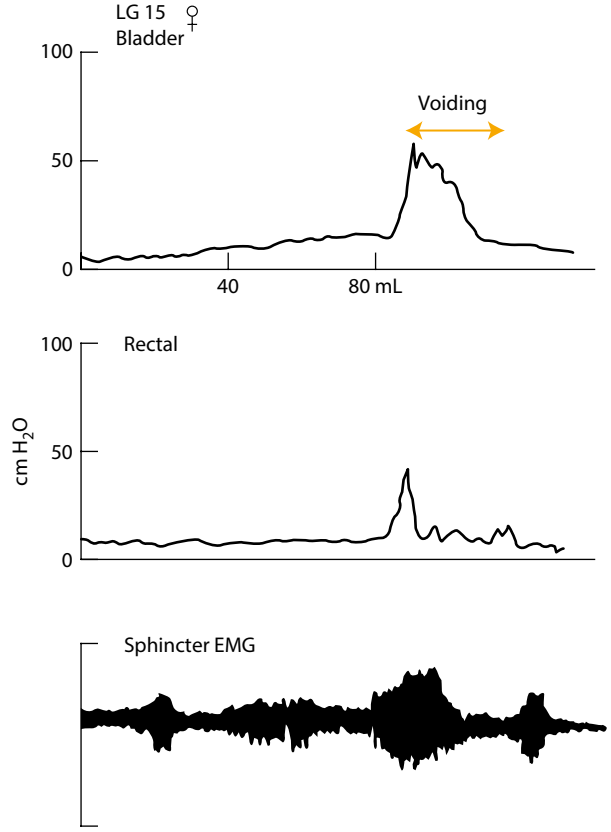

FIGURE 53.20 This urodynamic picture in a teenage female with recurrent infections reveals a small-capacity bladder and a hypertonic sphincter that relaxes only partially during voiding.

sphincter activity occurs all the time.[214] Jayanthi et al.[250] reported similar findings in a group of younger children, newborn to 30 months of age, and Bauer et al.[251] noted these same findings in five newborns and children under 1 year of age. All were managed by either vesicostomy, urinary diversion, or CIC, with spontaneous improvement after vesicostomy closure or urinary undiversion in some.

In general, children have urgency, urge and/or stress incontinence, infrequent voluntary voiding, intermittent urination associated with straining, recurrent UTI, and irregular bowel movements, with fecal soiling in between.[214] Most striking is the similarity in the pattern of family dynamics that is disclosed on carefully observing and questioning the parents.[249]

The Hinman syndrome has been applied to many children with any degree of voiding dysfunction, but it should only be diagnosed as such when most of the following conditions are present:

1. Clinical features
   a. Day and night wetting
   b. Fecal incontinence or constipation
   c. Recurrent UTIs
   d. Prominent parental themes
      i. Domineering or exacting
      ii. Divorce
      iii. Alcoholism
      iv. Punishments (mental and physical) inflicted for wetting
   e. Previous urologic surgery
      i. Ureteral reimplantation
      ii. Bladder neck plasty
      iii. Diversion
2. Radiologic features
   a. Hydronephrosis, with or without pyelonephritic changes
   b. Reflux: III–V in degree
   c. Large-capacity, trabeculated bladder
   d. Large residual urine volume
   e. Posterior urethra sometimes dilated with narrowing at EUS
   f. Colonic fullness
   g. Normal bony spine
3. Urodynamic features
   a. Elevated detrusor filling and voiding pressures
   b. Ineffective detrusor contractions
   c. High resting (but normal) sphincter EMG
   d. Unsustained sphincter relaxation during voiding
   e. Large residual volume.
4. Treatment (individualized)
   a. Bladder retraining
      i. Behavioral modification
      ii. Timed or double voiding
      iii. Biofeedback techniques for sphincter relaxation
      iv. CIC
   b. Drugs (anticholinergics, bladder relaxants, etc.) as detailed in the "general treatment strategies" section
   c. Bowel management
      i. Stool softeners
      ii. Bulking agents
      iii. Laxatives, enemas

A recent publication by Silay and colleagues suggests that children should meet all the following criteria for diagnosis of Hinman syndrome:[252]

1. LUT symptoms with daytime and/or nighttime incontinence
2. UTI with or without fever

3. Presence of any degree of hydronephrosis on initial ultrasound
4. Thickened bladder wall with trabeculations and dilated posterior urethra
5. Increased detrusor pressure and overactivity during filling
6. Inappropriate contractions of EUS during voiding
7. Normal anatomy and function of lower extremities
8. Absence of skin lesions overlying the sacrum
9. Intact perineal sensation and anal tone
10. Normal findings on spinal MRI
11. Absence of anatomic obstruction confirmed with cystoscopy

In the original conception of the syndrome, the parents, especially the father, are described as domineering, exacting, unyielding, and intolerant of weakness or failure. Divorce and alcoholism are common threads that only exacerbate the situation. Wetting is perceived as immature, defiant, and/or purposeful behavior that the parents feel must be counteracted with stern reprimands. The children are often punished, both mentally and physically, for their accidents. Confusion, depression, and withdrawal for fear of wetting, with its added punitive response, become the children's prevalent attitudes because they do not know how to, nor can they, prevent this provocative behavior. They try to withhold urination and defecation further by keeping the sphincter muscle tight, aggravating the situation. Thus, wetting becomes more commonplace, and abdominal pain from chronic constipation is likely.

Radiologic evaluation reveals profound changes within the urinary tract. Hydroureteronephrosis with or without pyelonephritic scarring from recurrent infection occurs in two-thirds of the children (Figure 53.21).[214] Fifty percent have severe VUR. Nearly every child has a grossly trabeculated, large-capacity bladder with a considerable postvoiding residual urine volume (Figure 53.21b). Voiding films show either persistent or intermittent narrowing in the region of the EUS in almost half of the children (Figure 53.21c). Finally, abdominal plain films display considerable fecal material in the colon, consistent with chronic constipation and a normal vertebral column.

Noninvasive uroflow reveals a staccato uroflow pattern. Residual urine varies from 0% to 50% of bladder capacity. Flow EMG demonstrates a urinary flow rate that is often intermittent as a result of the failure of the EUS to relax completely throughout voiding (Figure 53.22b). Invasive urodynamic studies demonstrate a large-capacity bladder with poor compliance, DO, and either high-pressure or ineffective detrusor contractions during voiding (Figure 53.22a).[214,225] Sometimes, Valsalva voiding is needed to empty the bladder. EMG recordings, however, reveal normal EUS innervation and exclude the possibility of a sacral spinal cord lesion. The sphincter fails to relax completely and may actually tighten episodically once voiding commences;[215] this finding, along with the premature contractions, suggests a UMN lesion, but usually, no other signs are present to confirm this urodynamic hypothesis. MRI has failed to reveal any intraspinal process as a cause for the voiding dysfunction in these children.[253]

The dyssynergy created by the incoordination between the bladder and sphincter muscles leads to high voiding pressures initially, and later to ineffective detrusor contractions.[215] Depending on which point of the spectrum one is at, a low or intermittent flow rate and either a minimal or significant postvoiding residual urine volume is noted.

Before this "syndrome" was recognized and the pathophysiology elucidated, many children underwent multiple operations to improve bladder emptying and correct VUR. Failure of these procedures to succeed led to urinary diversion in a number of instances. Some of these individuals were eventually able to be undiverted at an older age after they outgrew the conditions that caused their dysfunction in the first place.[254] Today, an entirely different approach is taken. Treatment is focused on improving the child's ability to empty the bladder and bowel and alleviating the psychosocial pressures that contribute to the aggravation of the voiding dysfunction. A frequent emptying schedule, accompanied by biofeedback techniques to relax the sphincter during voiding,[206,208] anticholinergic drugs to abolish DO, and improved bowel-emptying regimens, is instituted.[214] Despite these measures, CIC may be needed in children who fail to respond and in those individuals who require immediate decompression of their upper urinary tract.[232,255] In some cases, the outflow obstruction may have produced severe renal damage and even chronic kidney failure, which must be managed accordingly.

Psychotherapy is an integral part of the rehabilitative process to reeducate both the child and the parents in appropriate voiding habits. Punishments are stopped and a reward system is initiated in order to improve the child's self-image and confidence.[231] This comprehensive urotherapy approach provides the best means for rehabilitating the child's LUT and for preserving and maintaining renal health.[256]

SUMMARY

NBD is one of the more common severe problems in pediatric urology. The most frequent cause is neurospinal dysraphism, although there are many other etiologies. The treatment of NBD has been revolutionized by the introduction of CIC and targeted medical therapy, resulting in decreased morbidity and mortality and fewer children requiring invasive surgery. Children with neurogenic bladder should be serially monitored by clinical assessment, urodynamic testing, and urinary tract imaging, with treatment strategies adjusted based on the findings.

Functional voiding disorders are also commonly seen entities within pediatric urology. The symptoms can range in severity, and these disorders can cause urodynamic patterns similar to those seen in NBD. The evaluation should only include invasive testing in specific circumstances when noninvasive measures do not provide a clear picture of the patient's LUT function. Treatment strategies for functional voiding disorders are largely behavioral, although pharmacologic therapy and (occasionally) CIC are important adjuncts.

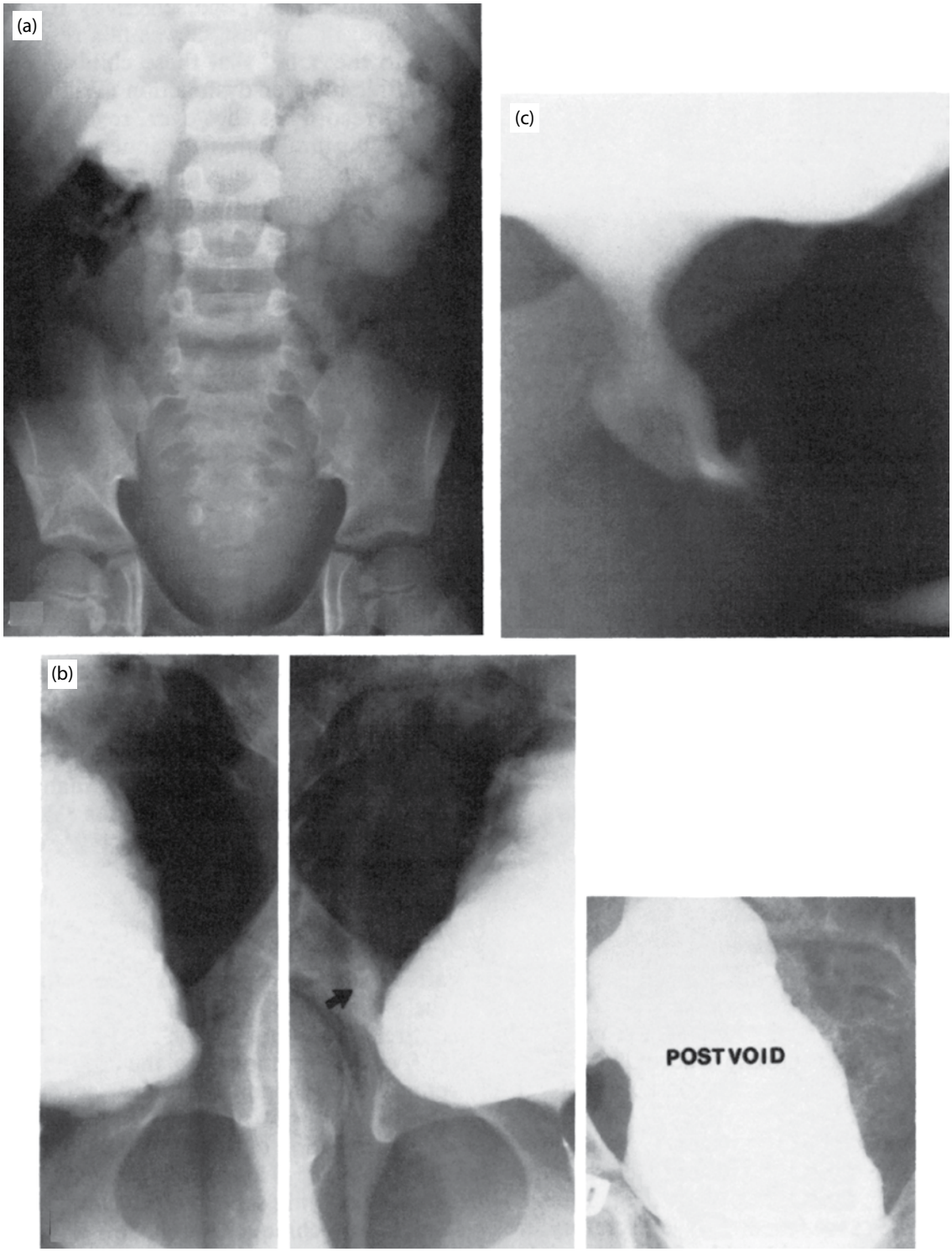

FIGURE 53.21 (a) Excretory urogram in a 14-year-old male with daytime and nighttime incontinence and encopresis. Note the impression of a faintly opacified distended bladder. (b) His voiding cystourethrogram reveals trabeculation, mild right vesicoureteral reflux (arrow), and a large postvoiding residual urine volume. (c) A film during voiding demonstrates intermittent relaxation of the external sphincter area.

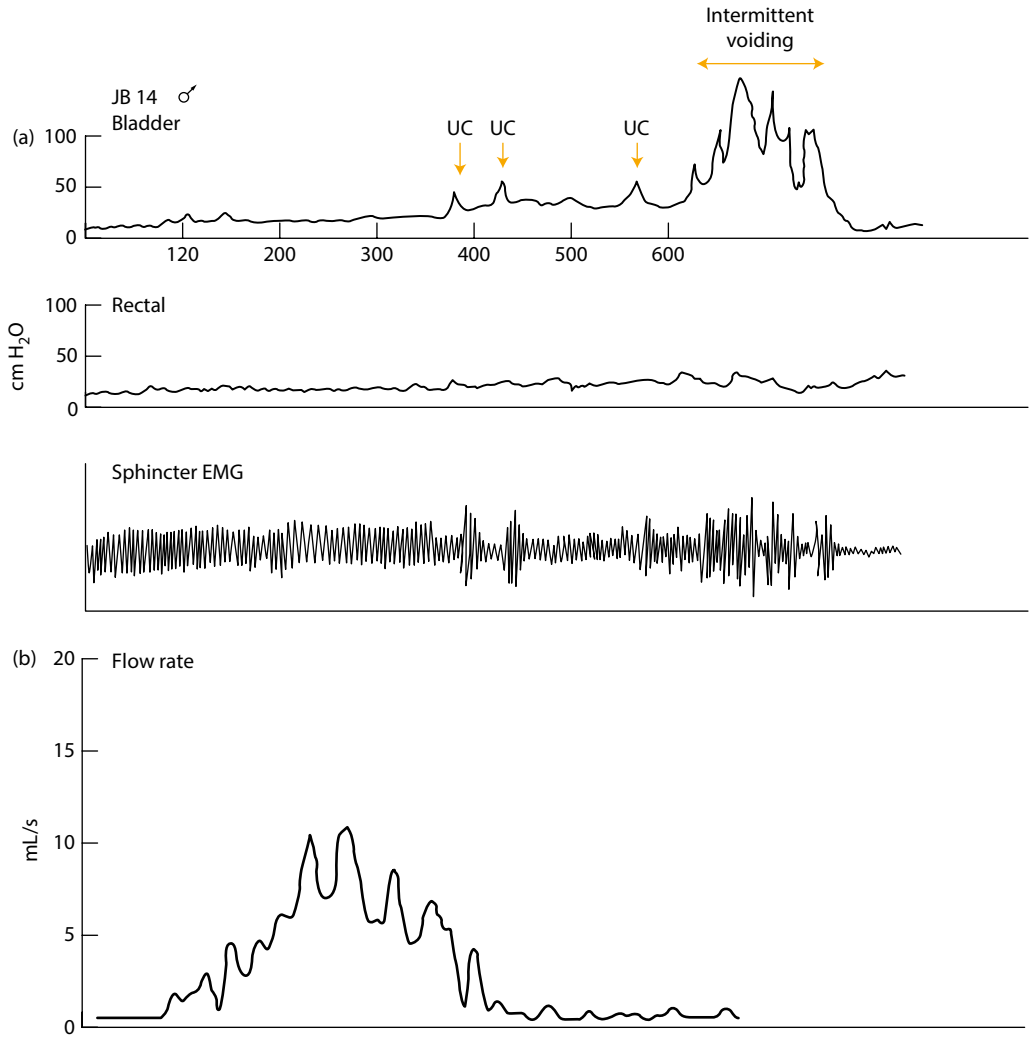

FIGURE 53.22 (a) Uninhibited detrusor contractions (UC) and increases in EUS EMG activity are noted as the bladder is filled. During voluntary voiding, very high bladder pressures (>100 cm H_2O) are generated owing to increased activity and then intermittent relaxation of the external sphincter. (b) The urinary flow rate reflects the voiding pattern seen on urodynamic evaluation.

MULTIMEDIA FILES AVAILABLE ONLINE (www.crcpress.com/cw/Docimo)

VIDEO 53.1 Bladder Botox™ procedure.

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CHAPTER 54

Diurnal and Nocturnal Enuresis

Mark Horowitz

DIURNAL ENURESIS

In the infant, a simple reflex controls bladder function without input from the supraspinal centers. A full bladder elicits a detrusor contraction via a signal that is sent along afferent pathways to the spinal cord, which then triggers the appropriate motor response, resulting in simultaneous relaxation of the external sphincter muscles. In the absence of an anatomic obstruction, this allows for low-pressure bladder emptying without resistance to flow. The adult pattern of urinary control evolves over time. During this transition, continence is achieved first by voluntary constriction of the external striated sphincter and later by supraspinal inhibition of bladder contractions. The ability to suppress detrusor contractions initially happens during the day, and then at night, and for this reason, children gain daytime continence prior to nighttime continence.

The adult pattern of voiding is characterized by the absence of bladder contractions, voluntary contraction of the external sphincter, and autonomic closure of the bladder neck during bladder filling. The events that occur during bladder emptying include opening of the bladder neck, relaxation of the external sphincter, and a sustained bladder contraction of adequate magnitude, resulting in complete emptying. Bladder capacity increases over time to permit it to function as an adequate-sized reservoir. In the first 2 years of life, the capacity can be estimated by multiplying the patient's weight in kilograms by 8, and this gives the capacity in milliliters. After 2 years of age, bladder capacity in milliliters can be estimated by the formula (Age [in years] + 2) × 30.[1] Deviation in the events of bladder filling and/or emptying result in voiding dysfunction.

Most children achieve day and night control by 4 years of age. The sequence of development of bowel and bladder control is in the following order: nocturnal bowel control, daytime bowel control, daytime urinary control, and nocturnal urinary control. Incontinence may be diurnal, nocturnal, or both. Patients with daytime incontinence often begin having symptoms 3–6 months after achieving urinary continence. The etiology of diurnal enuresis in most children is failure to relax their external sphincter during voiding, resulting in bladder hypertrophy and development of uninhibited bladder contractions (bladder instability). This activity of the pelvic floor muscles (external sphincter) during bladder contractions is known as detrusor sphincter dyssynergia (DSD). In many children, persistence of this learned behavior leads to voiding dysfunction. This dyssynergia between the bladder and external sphincter leads to high storage and voiding pressures, instability of the bladder, increased bladder wall thickness, high postvoid residual volumes, and recurrent infections. Isolated bladder instability in the absence of DSD may be secondary to bladder infection and dietary habits as well. There is a strong association between dysfunctional voiding and urinary tract infections (UTIs), as well as vesicoureteral reflux. Van Batavia and associates identified UTI in 33% of children treated for lower urinary tract dysfunction.[2] Reflux was found in 28% of patients that had an infection *not* associated with fever, and in 69% of those associated with fever. The incidence of infection was highest in patients with DSD and infrequent voiding.

Bladder instability leads to frequency and small voided volumes. More severe forms of this disorder were described as nonneurogenic neurogenic bladder or the Hinman syndrome.[3] Some of the features that were originally characterized by the Hinman syndrome included wetting during the day as well as at night, with fecal retention and soiling; UTI; radiological abnormalities of the bladder and/or kidneys; no demonstrable neurologic disease or bladder outlet obstruction; and improvement after reeducation and suggestive therapy. In addition to features seen in the Hinman syndrome, the Ochoa syndrome is associated with an unusual inversion of facial expression with smiling and a hereditary transmission. In both the Hinman syndrome and the Ochoa syndrome, upper tract damage may occur.

Enuresis is only one of many symptoms seen in the complex of voiding dysfunction. Other symptoms often elicited from patients with voiding dysfunction are urinary frequency, urgency, urge-associated incontinence, and other lower urinary tract symptoms (LUTSs). Additionally, many patients with voiding dysfunction exhibit signs and symptoms of bowel dysfunction, namely, constipation and encopresis. The term *dysfunctional elimination syndrome* has been used to describe patients with bladder and bowel dysfunction. Combs et al. retrospectively divided their patients with lower urinary tract dysfunction into three categories of bowel dysfunction: constipation, encopresis, and constipation plus encopresis. Constipation was the most common bowel dysfunction, being found in 27% of the patients, and 49% of all patients with dysfunctional voiding had some type of bowel dysfunction, i.e., constipation (39%), encopresis (6%), and constipation with encopresis (4%). Of the different types

of lower urinary tract conditions, bladder neck dysfunction had the lowest incidence of bowel dysfunction (19%).[4]

Daytime urinary incontinence represents a major source of concern for families and has potential to disrupt everyday life at home and school. Approximately 20% of children 4–6 years of age wet their pants, 3% wetting twice or more weekly.[5] As children get older, the incidence of enuresis declines but the wetting is less accepted by society and has a greater impact on their lives. Pediatric urologists are second in line to treat children with this problem, often after treatment failure by the primary caregiver. Our mission is to identify the source of the problem and offer specific solutions to improve the situation. It is important to remain minimally invasive and offer a treatment plan that is within reach of both the patient and his/her family, with minimal side effects. Enuresis secondary to neurogenic bladder (spina bifida) and anatomic causes (ureterocele, posterior urethral valves [PUVs], etc.) are not discussed.

Giggle incontinence (enuresis risoria) is the involuntary loss of urine induced by laughter. The cause is unknown, and there are minimal treatment modalities that are effective. The upper tracts are not affected. Chandra et al.[159] reported on a large cohort of children with giggle incontinence, of which 95% had concomitant dysfunctional voiding symptoms. They concluded that this entity is caused by detrusor instability, and therapy should include timed voiding, anticholinergic therapy, and a bowel program. They reported an 89% remission rate within 10 weeks. Some have reported success with the use of methylphenidate (Ritalin).

Constipation and Enuresis

Until proven otherwise, all patients with lower urinary tract disorders have constipation. Constipation is defined by the hard nature of the stool, the pain associated with its passage, or the failure to pass three stools per week.[6] Voluntary withholding of feces, most of the time caused by fear of painful defecation, is the most common cause of constipation. Encopresis or fecal soiling occurs when loose stool leaks per rectum after passing retained harder stool. Children with encopresis hide their underwear even more so than children with urinary incontinence. Because of the close proximity of the bladder to the rectum, impacted stool in the rectum does not allow the bladder to fill to capacity. Patients void smaller amounts with greater frequency and have elevated postvoid residual volume secondary to incomplete relaxation of the pelvic floor muscles during voiding, which may lead to UTIs. Patients with severe constipation and/or encopresis are often found sitting in the corner of a room, holding in a bowel movement. The frequency of bowel movements and consistency of the stool must be included in the history. Parents often know the voiding pattern of their children and the number of urinary and fecal accidents but have little knowledge of their children's frequency of bowel movements.

Treatment of constipation may help to eliminate bladder instability secondary to compression of the bladder base by a large bolus of feces. Loening-Baucke correlated resolution of voiding dysfunction symptoms with treatment of constipation.[7] Within this study, successful treatment of constipation led to resolution of daytime incontinence in 89%, nighttime incontinence in 63%, and UTI in 100% of patients. They recommended reconditioning the child's bowel movements with timed attempts to defecate, teaching proper toilet sitting positions, and modifying dietary habits. Failure to diagnose and treat constipation often hinders the success of therapy for voiding dysfunction. Initial therapy is aimed at adding more fiber to the diet in the form of high-fiber foods, fiber additives, or laxatives, which make bowel movements soft and easy to pass. Treatment options include the use of enemas, fecal disimpaction, and a variety of oral agents, such as Miralax, mineral oil, milk of magnesia, and sorbitol.

The length of treatment may extend beyond that recommended, depending on the patients' clinical response:

1. Mineral oil alone, 15–30 mL/kg/day, up to 8 ounces once or twice daily for 3 days
2. Hypertonic enemas and/or suppositories daily for 2–3 days
3. Polyethylene glycol 3350 (Miralax) orally, up to 1.5 g/kg/day to a maximum of 100 g for 3 days
4. An enema each day for 2 days, followed by milk of magnesia, 1 cc/kg/dose twice daily for 3 days

Following the initial cleanout, maintenance programs keep the patient defecating on a regular basis. Stool softeners used for a prolonged period include

- Milk of magnesia (1–4 mL/kg/day)
- Mineral oil (2–6 mL/kg/day)
- Sorbitol or lactulose (0.7–3 mg/kg/day)
- Polyethylene glycol 3350 (0.27–1.42 mg/kg/day)

WORKUP

The most important aspect in the workup of a patient with incontinence is the history. A thorough, systematic approach is critical in defining the cause and directing the treatment. Most anatomic and neurogenic causes of incontinence can be ruled out by a careful history and physical. The following is a list of questions routinely asked of patients or families of children with daytime incontinence.

- How long has the wetting been a problem? We are more inclined to proceed with a full workup in a patient that has been having accidents for several months than someone who started having accidents a week before their visit. Often symptoms will resolve without intervention if given some time.
- How significant is the wetting? Do they soak through their clothes, or is there simply a stain on the underwear? Many parents only consider soaking episodes or wetting that requires a change of underwear to be incontinence and accept dampness as either normal or inconsequential. Once children get old enough to change their own clothes, parents are often unaware

of the wetting problem. Many children, boys and girls, drip urine because they are in a rush and pull up their clothes before letting all the urine out. These children simply need to spend an extra couple of seconds to complete the process of voiding. Boys are instructed to shake their penis so that the urine in the urethra does not drip into their underwear.

- How often do they void? Some parents complain that their children go very frequently, but with further questioning, these children can sit through a movie or participate in a sporting event without the need to void. A voiding diary for several days eliminates some of the confusion we encounter with conflicting answers between parent and child. They record how often they go and what volumes are voided each time they go. It is easier to do this over the weekend than during the week when the child is at school. The normal frequency of voiding in a child is four to seven times per day or about every 2–3 hours. Children who void eight or more times per day or more frequently than every hour and a half have increased frequency. Voiding patterns are determined by a combination of physiological, behavioral, and social factors. Many children void two or three times a day, and it is these children that often do not urinate upon awakening. Bladder infections are commonly seen in this group.
- Are they more symptomatic at home or at school? Some children are fine at school, where they go two or three times during the day, but have urgency and accidents once they get home because they do not want to void while involved in other activities (watching television, playing with friends, and playing computer games). Others wet at school because the teachers will not let them use the bathroom, and some are afraid to use public restrooms (lack of privacy, poor sanitary conditions, and violence in the bathrooms). These children usually come home wet from school but after school and on the weekends are able to stay dry.
- Are there associated bladder or kidney infections? If yes, try to figure out if the patient's symptoms started after an infection, or did the patient have symptoms that led to an infection (high postvoid residual volumes and/or high-pressure voiding with turbulent flow). The volume of residual urines correlates well with the frequency of UTIs.[8]
- Do the accidents happen all the time or only when associated with certain conditions? Stress at home or in the school may cause daytime accidents.
- Is the flow continuous with a good stream, or is it choppy and slow? Is there a straining pattern? Do they feel like they empty their bladder or have to go shortly after voiding? Although not discussed in this chapter, PUVs, meatal stenosis, and stricture disease can cause a poor stream and must be considered.
- How much fluids are consumed over a 24-hour period? LUTSs may be improved by reducing total intake. Patients are instructed to drink enough to keep their specific gravity between 1.010 and 1.020.
- Other than incontinence, are there other LUTSs? Most children complain of urinary urgency, and many do not feel a warning or urge before becoming wet. In an attempt to stay dry, many girls either squat and sit on the heel of one foot (Vincent's curtsy) or cross their legs. This squatting behavior is a unique learned response to a sudden detrusor contraction and is an attempt to minimize the amount of incontinence. Boys sometimes grab their penis to stay dry.
- What does the urine typically look like, and does it have a discreet smell? Dark yellow, strong-smelling urine indicates a relatively dehydrated state or the presence of infection. Patients are encouraged to drink more or void with greater frequency. If present, infections should be treated with antibiotics. Cranberry and cherry juice (or tablets) help to prevent infections. Bacterial cystitis should be suspected when symptoms include dysuria, cloudy, foul-smelling urine and visible blood or mucus in the urine.

The Dysfunctional Voiding Scoring System Questionnaire (DVSSQ) is a reliable tool used for diagnosing and monitoring treatment of children with voiding dysfunction. Doubrava and Bartkowski performed uroflow with pelvic floor electromyography (EMG) and postvoid residual (PVR) measurements on 51 patients with normal DVSSQ scores for gender.[9] The DVSSQ was able to predict a normal bell-shaped uroflow curve in 73% of patients; however, it correlated poorly with EMG patterns and PVR volumes. Of patients with normal DVSSQ, 65% had abnormal EMG patterns, and there was poor correlation between uroflow curves and EMG patterns, as well as between uroflow patterns and PVR values.

DYSFUNCTIONAL VOIDING SYMPTOM SCORE

Over the last month

1. I have had wet clothes or wet underwear during the day.
2. I wet the bed at night.
3. When I wet myself, my underwear is soaked.
4. I do not have a bowel movement every day.
5. I have to push for my bowel movements to come out.
6. I go to the bathroom only one or two times each day.
7. I can hold on to my pee by crossing my legs, squatting, or doing the "pee dance."
8. When I have to pee, I cannot wait.
9. I have to push to pee.
10. When I pee, it hurts.
11. Parents to answer: Has your child experienced any of the following in the past year: new baby, new home, new school, school problems, abuse (sexual or physical), divorce or death, special events (birthday), accident, injury, or other stressful event?

Questionnaires are the most practical method for measuring the magnitude of incontinence, and many questionnaires exist for evaluating and following children with incontinence. Most take just a few moments to complete and should be used in the evaluation of all patients with daytime wetting. It is easy to overlook certain parts

of the voiding history. It is therefore recommended to choose the questionnaire that you feel most comfortable with and incorporate it into the patient's medical record. Sureshkumar et al. developed a daytime urinary incontinence questionnaire using parent reported data and demonstrated that it is reproducible.[10] The questionnaire was used in a prevalence survey of Australian primary school children to determine the magnitude of the problem in those starting school. Farhat et al. evaluated the performance of an objective instrument to quantify or grade the severity of abnormal voiding behaviors in children.[11] There are 10 voiding dysfunction parameters that are assigned a score of 0–3 according to prevalence, and scores range from 0 to 30. These questionnaires and others help to identify patients with dysfunctional voiding and further their investigative studies and treatment.

PHYSICAL EXAMINATION

Emphasis should be placed on the physical examination in the assessment of the child with voiding dysfunction. Special focus should be placed on evaluation of the abdomen, genitalia, and back. Inspection of the lower back for evidence of skin discoloration, dimples, hair patches, subcutaneous lipomas, or spine defects may indicate the presence of an underlying spinal dysraphism. Asymmetry of the buttocks or motor tone of the buttocks may also indicate the presence of a neurologic disease. An absent or asymmetrical gluteal cleft suggests sacral agenesis. The neurologic examination includes careful attention to the lower extremities, including strength, sensation, reflexes, and assessment of the child's gait. If there is any concern for the presence of a neurologic etiology, consideration should be given toward obtaining an MRI of the lumbosacral spine or requesting a full neurologic examination. Patients with definite abnormalities, such as tethered cord or lipomas, may require neurosurgical intervention. Most patients with spina bifida occulta and a normal spinal cord will experience resolution of their enuresis with conservative management. Ritchey et al. compared outcomes for enuretic children with spina bifida occulta with those for enuretic children with normal spine x-rays.[12] The majority of patients in both groups had resolution of the enuresis with conservative management, and only a small percentage of children with spina bifida occulta required neurosurgical intervention.

Examination of the external genitalia may reveal the source of the problem. Boys with significant meatal stenosis may present with LUTSs, mainly a decreased stream, deflection of the stream, urinary hesitancy, and incontinence. Observation of the urinary stream and uroflowmetry are more objective methods to assess the functional significance of meatal stenosis. Girls with labial fusion may present with LUTSs, including dysuria, dribbling, and incontinence. Examination of the vaginal introitous may reveal a ureterocele or an ectopic ureter. Girls with continuous incontinence between normal voids should be suspected of having an ectopic ureter. Rashes on the genital area or inner thighs may indicate constant exposure of the skin to urine. Skin bacteria break down urine and lead to urea burns. Girls with vaginal voiding often present with labiovulvar erythema and/or leukorrhea that may cause burning and itching.

It is important to assess the child's undergarments. It is common for parents to claim that their child is always wet, and when examined, they are found to be dry. When asked to explain this inconsistency, the parents state that the child voided just before coming to the office. It is clear that if he or she voids frequently, wetting can be avoided. Fecal stains suggest the presence of constipation or encopresis.

A urinalysis is obtained in all patients looking for infection, proteinuria, or glycosuria. A catheterized specimen is obtained for culture and sensitivity if a voided urine culture is positive.

Uroflowmetry, because of its noninvasive nature, is an important tool for evaluating the lower urinary tract. It has been suggested that it is the perfect instrument for revealing voiding disorders in pediatric patients.[13] Patients are instructed to void when they have a "normal" desire to void, and parameters measured include peak flow rate, average flow rate, amount voided, and the shape of the curve. Voided amounts significantly affect the peak and average flow rates. Volumes of less than 50 mL are seldom considered relevant for interpreting uroflowmetry. Gupta et al. determined flow rates and generated flow rate–voided volume nomograms based on healthy children 5–15 years old voiding spontaneously in their natural environment.[14] There were no significant differences noted in uroflow rates from 5 to 10 years, and then again from 11 to 15 years. Their nomograms will hopefully promote wider application of flow testing in the pediatric population. We have found this simple test to be useful in identifying patients with decreased expected capacity for age that might benefit from pharmacotherapy. We instruct our patients to void when they feel full, and if their voided volumes are persistently low for age, we have them keep a voiding diary at home. If their voided volumes at home are low as well, we add anticholinergic therapy to their regimen.

Simultaneous measurement of uroflow rates and pelvic floor EMG tracings (flow/EMG) have been incorporated into the initial assessment of almost every patient we evaluate for daytime incontinence and bladder or kidney infections. The normal, coordinated flow curve is even and bell-shaped in the absence of pelvic floor activity (Figure 54.1). By contrast, voiding with an active pelvic floor results in a ragged curve shape, the so-called staccato, interrupted, or irregular curve.[15] EMG studies typically show increased activity during voiding, instead of the expected relaxation (Figure 54.2).

Combs et al. reported on the utility of pelvic floor EMG lag time in identifying children with detrusor instability.[16] Pelvic floor EMG lag time is the time interval between pelvic floor relaxation on pelvic floor EMG and the start of flow. Pelvic floor relaxation occurs 1–4 seconds prior to the start of a voluntary detrusor contraction and the start of flow. Urine flow that occurs instantaneously with or prior to relaxation of the pelvic floor indicates instability (Figure 54.3). Urodynamics confirmed the presence of instability in all patients that had a lag time that approaches zero or is in the negative range.

Bladder ultrasound is performed to document postvoid residual volumes and record bladder wall thickness and/

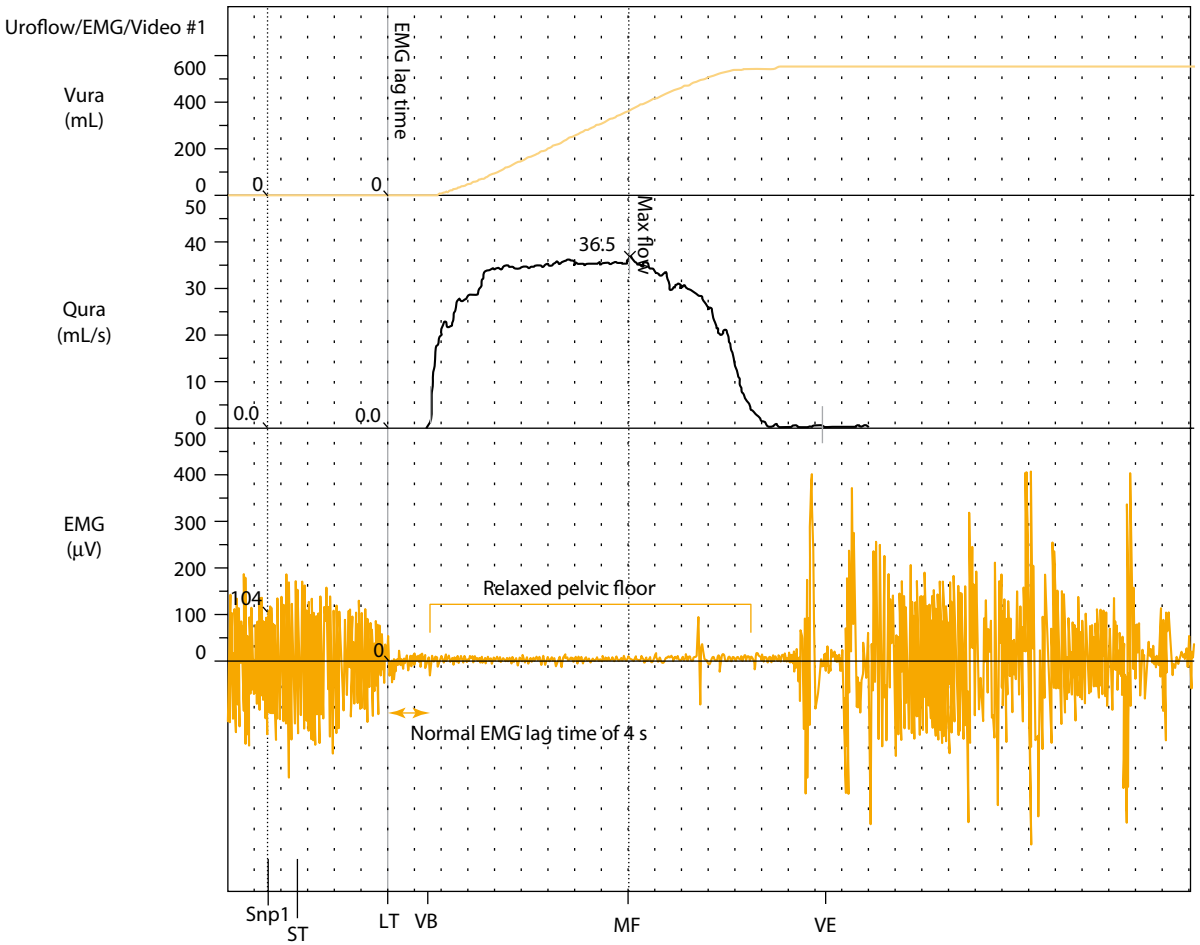

FIGURE 54.1 Normal voiding pattern. Electromyography (EMG) lag time of 4 seconds. Complete relaxation of pelvic floor muscles with voiding. Normal bell-shaped uroflow curve. V_{ura}, volume of voided urine; Q_{ura}, urine flow; ST, start/stop; LT, lag time; VB, voiding begins; MF, maximum flow; VE, voiding ends.

or distal ureteral dilatation. If hydronephrosis is seen on prevoid images, we document resolution, improvement, or no change in the hydronephrosis after the patient voids. Bladder wall thickness should be evaluated only with the bladder full. Increased bladder wall thickness implies detrusor hypertrophy, which is secondary to the bladder working against tightened pelvic floor muscles during voiding. The upper tracts are usually normal in patients with voiding dysfunction, and a renal sonogram is a quick, noninvasive, inexpensive screening tool to rule out most genitourinary anatomic anomalies.

Cystography is often used to look for reflux in a child with a UTI. Other parameters looked at are postvoid residual volumes, urethral anatomy to identify bladder outlet obstruction (PUVs, stricture, and DSD), and bladder capacity. Bladder instability can be detected when at least one of three well-defined radiological signs is detected. These signs include bladder wall irregularity, elongation of bladder shape, and filling of the posterior urethra. The chances of identifying these signs are greatest if films are exposed when unstable contractions occur, which implies that spot fluoroscopy has to be performed more often. Passerini–Glazel et al. considered this process a typical and constant sign of bladder instability.[17] Symptoms of instability are easy to elicit from older children; however, the history has limited use in infants and younger children. In these patients, bladder instability can be recognized on voiding cystourethrography (VCUG) if cystography is indicated.

Kakizaki et al. measured the internal diameter of the external urethral sphincter by VCUG in children with and without suspected voiding dysfunction to evaluate its diagnostic accuracy as a predictor of detrusor sphincter incoordination.[18] A diameter of less than 3 mm had satisfactory sensitivity and specificity for detecting detrusor sphincter incoordination.

We have substituted videourodynamics (VUDS) for VCUG in patients with LUTSs in association with documented UTIs and in those not responding to conventional therapy. The advantages of VUDS over VCUG include assessment of detrusor pressures during filling and emptying and the ability to limit radiation exposure. Monitoring bladder pressures continuously allows us to limit the use of fluoroscopy. We get spot images at the start of the study, two to three times during filling (usually at 25%, 50%, and 75% of expected capacity for age), and when we see unstable bladder activity on cystometry. Burst images are then taken during voiding and a single image taken to document PVR. This is less exposure than used during VCUG, where multiple spot images are taken

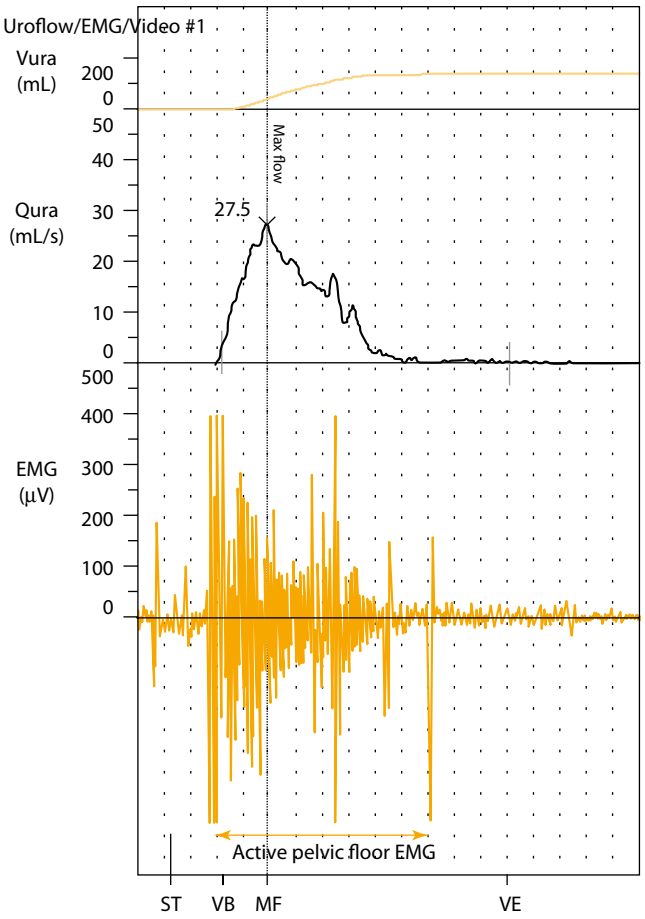

FIGURE 54.2 Type 1 dysfunctional voiding pattern. Persistent activity (nonrelaxation) of pelvic floor muscles during voiding with a staccato uroflow curve.

to look for signs of instability. The added parameters obtained during VUDS, namely, filling pressures, voiding pressures, and EMG activity of the pelvic floor during voiding, help direct us in the management of patients with more specific therapy. Simultaneous EMG activities are recorded during VUDS, and repeat noninvasive flow/EMGs are used to monitor the patient's response to therapy. Other patients studied are those with a history suggesting anatomic problems, i.e., PUVs, or those in whom conventional therapy has failed. Primary bladder neck dysfunction (PBND), PUVs, urethral stricture, and meatal stenosis should be considered in boys with poor uroflow rates despite a relaxed pelvic floor, and VUDS can aid in defining the etiology of the findings. Bladder neck dysfunction patients exhibit narrowing at the bladder neck, in addition to high voiding pressures and low flow rates with an obstructive pattern. Some patients are able to maintain high enough voiding pressures to achieve normal flow rates. Studies typically show detrusor instability and high voiding pressures. In patients with a long history of LUTSs, we may see impaired compliance and/or inefficient detrusor contractions. Urinary flow is often intermittent, and there is often a prolonged opening time, which is defined as the time between the start of a contraction and the start of urine flow. Pelvic floor EMG lag time has been shown to correlate nicely with the opening time seen on VUDS.[19] Prolonged pelvic floor EMG lag time associated with abnormal uroflowmetry is highly suggestive of PBND (Figure 54.4). There may be a disparity between peak pressure and peak flow.

TREATMENT OPTIONS

The first step is having the child void on a timed schedule. Patients are instructed to void every 2–3 hours during the day, even if they do not feel the urge to void. A multiple-alarm watch is a helpful novelty to remind a child to go to the bathroom. A letter is sent to school stating that the patient is being treated for a urologic problem and needs to be reminded and allowed to go to the bathroom every 3 hours. Timed voiding requires a great deal of cooperation by the parents, teachers, and child. In addition to timed voiding, the child must spend at least 30 seconds to one minute voiding and must relax to ensure efficient emptying. Rewards (stickers, gold stars, etc.) are given each time the patient performs satisfactorily. Girls are instructed to pull their pants or skirts down to their ankles and sit with their legs apart. Toilets are designed for adults, and the one-size-fits-all concept is not suitable for a child. When a child sits on an adult-sized toilet, the child cannot relax the pelvic floor muscles. Girls with vaginal voiding experience postvoid dribbling. Urine that enters the lower vagina leaks into the underwear when they stand up. Toilet seat adaptors and footstools should be available at both home and school. Girls are instructed to sit backwards on the toilet (straddling the toilet seat) to help relax the pelvic floor muscles. At times, measuring and recording voided volumes may be added to the routine.

Patients who develop acute onset of severe frequency (more than once an hour) have nothing to gain by voiding every 3 hours. Severe frequency in the absence of burning, dysuria, or incontinence is often self-limiting and can last for many months. Anticholinergic medications have little role in the treatment.

Patients with LUTSs often require pharmacologic therapy in addition to timed voiding. The common view is that in overactive bladder, the drugs act by blocking the muscarinic receptors on the detrusor muscle, which are stimulated by acetylcholine released from activated cholinergic (parasympathetic) nerves. Anticholinergic medications act mainly during bladder filling, decreasing urge and increasing bladder capacity. In the dose range needed for beneficial effect in the overactive bladder, there is little evidence for a significant reduction of the voiding contraction during bladder emptying.[20] Ditropan is a potent anticholinergic agent with strong independent smooth muscle antispasmodic activity at a site distal to the cholinergic receptor. In young children who cannot swallow pills, we initiate treatment with Ditropan suspension two or three times a day. Children who can swallow are started on Ditropan XL once a day. Patients on Ditropan experience a decrease in the frequency and intensity of uninhibited bladder contractions. Reported side effects that are more common in the summer months and with the suspension preparation of the drug include dry mouth and flushing.

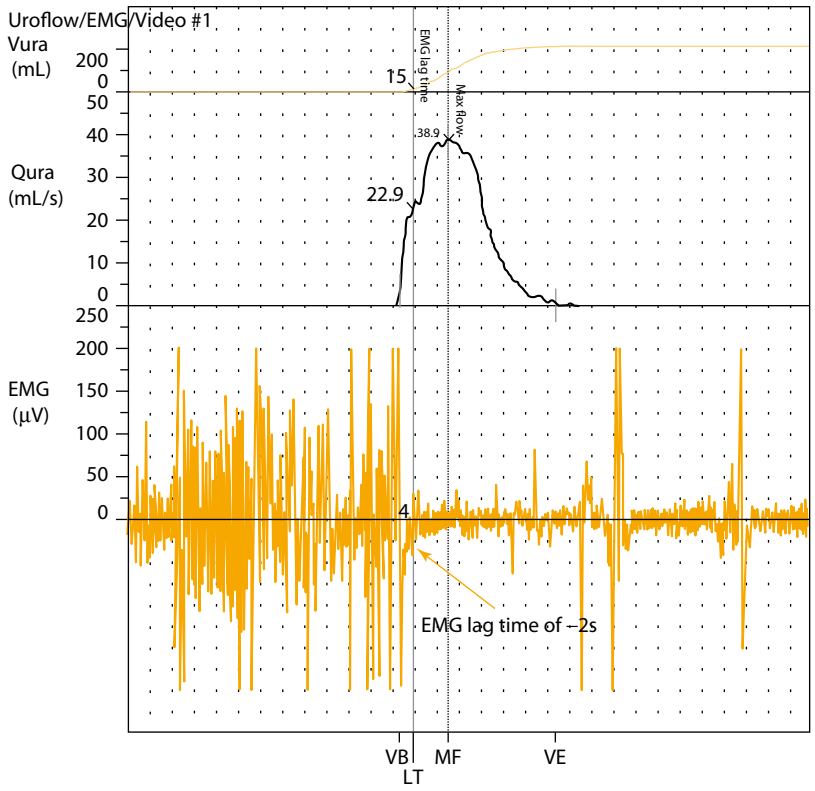

FIGURE 54.3 Type 2 dysfunctional voiding pattern (bladder instability). No lag time noted, which indicates initiation of flow prior to relaxation of pelvic floor muscle activity. Vura, volume of voided urine; Qura, urine flow; ST, start/stop; LT, lag time; VB, voiding begins; MF, maximum flow; VE, voiding ends.

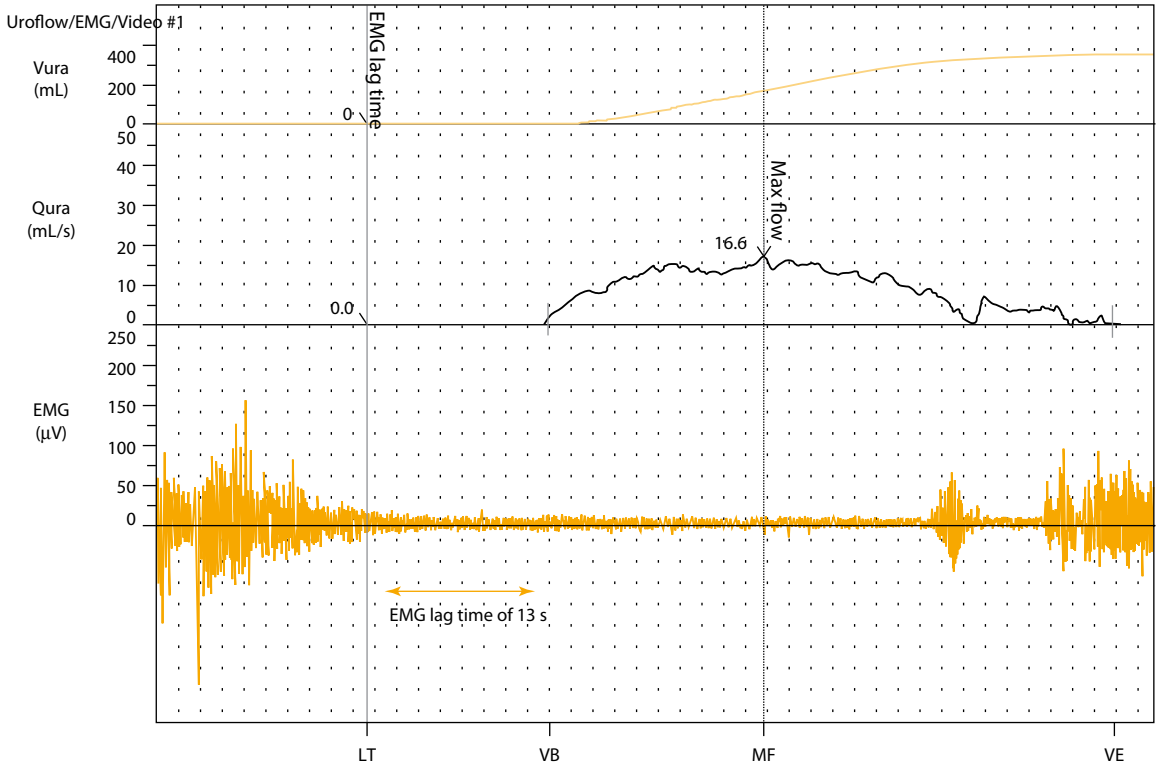

FIGURE 54.4 Bladder neck dysfunction. Lag time of 10 s (normal lag time = 2–4 s). Complete relaxation of pelvic floor muscles with voiding.

Ditropan decreases the natural ability to sweat, which can cause overheating in the very active child in extreme climates. Other side effects include dizziness, blurred vision, and excessive sleepiness. The medication is more effective on an empty stomach, so patients are instructed to take Ditropan either 30 minutes before a meal or an hour after meals. If patients have not already restricted their fluid intake, they are instructed to do so to maximize the voiding interval. Many patients are instructed to drink plenty of fluids to avoid infection and minimize the side effects of Ditropan, which gives them mixed messages.

The above-mentioned therapeutic strategy is considered simple behavioral therapy without biofeedback. Wiener et al. reported on the long-term efficacy of simple behavioral therapy for daytime wetting in children.[21] Formalized management of bowel elimination was not included. There was improvement in daytime urinary control in 59.4% at a mean of 4.7 years after completion of therapy. Frequency and urgency demonstrated long-term improvement in 51% and 46%, respectively. Assessment of symptoms during the first year after therapy revealed similar results, with 73% reporting improvement at 12 months. Behavioral therapy may lose some efficacy with time without return visits to reinforce therapeutic interventions. They concluded that simple behavioral therapy without biofeedback should be first-line therapy for children with daytime incontinence.

Biofeedback is the use of modern instrumentation to give a person better moment-to-moment information about a specific physiologic process that is under control of the central nervous system, but not clearly or accurately perceived. With biofeedback, patients can be made aware of and gain control over certain bodily functions. Biofeedback therapy is very successful in the treatment of voiding dysfunction. It can be used alone or in combination with other treatment modalities discussed in this chapter. With respect to voiding dysfunction, biofeedback teaches the patient how to relax the pelvic floor muscles during voiding, thereby improving flow parameters and decreasing postvoid residual volumes. To be successful, patients should be attentive and motivated so they can be taught to isolate the pelvic floor muscles. The success of biofeedback depends on patient and parent compliance, as well as on careful patient selection based on the motivation to learn and participate in the program. Few patients are cured with a single session of biofeedback. Most patients require several sessions, the number determined by improvement using clinical and urodynamic criteria. Each session starts with a review of the prior session; review of symptoms, with special emphasis on improvement or deterioration of LUTSs and incontinence; and review of current medications. Biofeedback is time-consuming for clinicians, children, and families, which may lead to problems with compliance.

Nelson et al. reported on the use of biofeedback in 81 patients with voiding dysfunction in whom conservative management failed.[22] Of 73 patients with incontinence, 30% became dry, 49% improved, and 21% had no change after biofeedback. Recurrent UTIs resolved in 78% of patients. Noninvasive urodynamics after therapy showed a significant increase in maximum and average flow rates and a significant decrease in postvoid residual volumes. Children were taught to void with a more normal flow pattern and greater voiding efficiency, even in the absence of improving continence.

Herndon et al. reviewed their experience with a conservative medical program and computer-assisted pelvic floor muscle retraining in patients with voiding dysfunction.[23] Patient compliance with the program was reported at 95%, and subjective improvement was seen in 87% of the group. Predictors of failure included a bladder capacity of less than 60% of the predicted volume and patient noncompliance. With adding medications, 83% of the nonresponders improved.

Kajbafzadeh et al. evaluated the efficacy of animated biofeedback in bowel and voiding dysfunction in 80 children with dysfunctional elimination syndrome.[24] Half the group of patients received animated biofeedback in addition to behavioral modification (hydration, high-fiber diet, and scheduled voiding), and the other half underwent behavioral modification only. They found that animated biofeedback in combination with pelvic floor exercises resulted in promising improvements in subjective and objective manifestations of dysfunctional voiding, as well as notable resolution of bowel dysfunction, vesicoureteral reflux, and recurrent UTIs.

Different methods of direct sacral nerve stimulation have been used to treat refractory lower urinary tract dysfunction in adults. The invasive nature of this procedure precludes its use in children. In contrast, genital, anal, intravesical, and percutaneous tibial stimulation have been reported in children. However, these techniques require either genital manipulation, placement of an anal probe, bladder catheterization, or needle insertion, all considered somewhat invasive in children. De Gennaro et al. reported on percutaneous tibial nerve stimulation in children and found it to be minimally invasive and feasible in children.[25] There was improvement in micturition symptoms, incontinence, flow rates, and PVRs with no adverse effects.

PBND is a fairly new entity that has received much attention in the past few years. Perhaps it is one of the entities that had a treatment prior to knowing what we were actually treating. On VUDS, it is characterized by the constellation of prolonged opening time, incomplete bladder neck funneling, quiet pelvic floor EMG during voiding, and abnormal pressure flow parameters. As mentioned earlier, the diagnosis can be made with noninvasive uroflowmetry combined with pelvic floor EMG.

Alpha-blocker therapy is being used with greater frequency in patients with voiding dysfunction. Austin et al. were one of the first groups to investigate the role of alpha-blockers for the management of incomplete bladder emptying in children.[26] They looked at 17 children with documented poor emptying due to various etiologies, including both neurogenic and nonneurogenic causes. With the use of an alpha 1-adrenergic receptor antagonist, bladder symptomatology and/or emptying improved in 82% of patients and was well tolerated by most. Because of this success, they looked at a larger group of 55 patients with voiding dysfunction and poor bladder emptying.[27] There was an 88% reduction in the pretreatment PVR volume, with only three patients showing no change in PVR. There was improvement in diurnal continence in 83% of

patients and urgency in 70%. They concluded that selective alpha-blocker therapy might be used as either replacement for or in addition to biofeedback in patients with significant PVRs. At this time, alpha-blockers have yet to be Food and Drug Administration (FDA) approved and are being used off-label.

Yucel et al. compared the efficacy of biofeedback and alpha-blocker therapy in children with PVR who had symptoms of incontinence, urgency, and UTIs.[28] There was no statistical difference between the two arms ($p > 0.05$) when looking at posttreatment reduction in PVR as the end point. Combined treatment of biofeedback and alpha-blocker helped 83% of the children with refractory high PVR treated with either biofeedback or alpha-blocker therapy alone. A group that responds nicely to alpha-blockers is children with PBND. Donohoe et al. used alpha-blockers to treat 26 patients with PBND.[29] With alpha-blockers, average and maximum flow rates improved from 5.5 to 12.6 cc/second and from 10.3 to 19.7 cc/second, respectively. Postvoid residual volumes decreased from 98.9 to 8.9 cc ($p < 0.001$). No patient experienced any major adverse side effects.

Kajbafzadeh et al. evaluated the effect of prazosin on vesicoureteral reflux resolution and urodynamic parameters in 62 children with idiopathic primary reflux and PBND.[30] Patients with documented reflux and urodynamics-proved primary PBND were randomized to receive either an alpha-blocker or placebo. In the placebo group, no uroflowmetry or urodynamic parameters changed significantly at 1-year follow-up. They observed a 60% decrease in reflux grade in the treatment grade compared with 17% in the placebo group. Significant decreases in maximal detrusor pressure, postvoid residual volumes, and opening time were seen in the treatment group, as was improvement in average flow rates.

Diet can have a profound effect on voiding patterns, and dietary changes can alleviate symptoms associated with bladder dysfunction. Avoiding the 4Cs (caffeine, chocolate, carbonated beverages, and citrus beverages) is an integral part of therapy, as they are known to cause urgency, frequency, and/or incontinence.

Clean intermittent catheterization (CIC) is a last option in a subset of patients that do not respond to standard treatment modalities. Alpert et al. reported their experience with 20 patients requiring CIC.[31] CIC was an easy technique for 80% of the children to learn in a single visit and master in a short period of time. If necessary, CIC is often used as a temporary measure until the patients can be taught to void in a correct manner. When all these modalities have been tried and failed, surgical intervention may be necessary. Augmentation cystoplasty with CIC will provide a large-capacity, low-pressure, compliant bladder that allows for preservation of renal function and urinary continence. However, this is a long haul for a problem with no neurologic or anatomic etiology.

There are numerous approaches for the treatment of urinary incontinence in children. The aggressiveness of evaluation and intervention usually depends on the age of the patient, chronicity of the problem, and other associated issues, such as recurrent infections. A systematic review of randomized controlled trials led to the conclusion that there is lack of proof for optimal treatment of pediatric incontinence.[32] Historically, antimuscarinic drugs have been the first line of treatment for urinary urgency, frequency, and urge-associated incontinence. Although associated with side effects that limit their use in some children, these drugs have undisputed effectiveness in the treatment of the overactive bladder. These medications are better tolerated with the advent of once-a-day formulation. They are often used in combination with other treatment modalities, including alpha-blockers, antibiotics, and bladder and bowel retraining. Newer once-daily M3-selective receptor antagonist agents are now available for treatment of the overactive bladder. With greater affinity for the M3 receptors than the M1 and M2 receptors, there is less dry mouth and less constipation. There are also significantly less central nervous system and cardiac side effects. The use of botulinum types A and B toxin injections into the detrusor muscle has been studied extensively for the treatment of incontinence due to neurogenic causes. These treatments are safe and minimally invasive and can be injected repeatedly but to date have had no role in the treatment of nonneurogenic voiding disorders.

SUMMARY

Voiding dysfunction is a common childhood problem. Use of a checklist for both the history and physical examination is highly recommended. Patience, diligence, and consistency are critical in the evaluation of these patients. Most children will respond to simple measures, such as timed voiding and relaxation techniques to facilitate bladder emptying. A select population of patients in whom single-modality therapy fails, multiple-modality therapy, including timed voiding, biofeedback, and medications, is advised. In our experience, almost all patients can be treated successfully with combination therapy. The objective improvements we aim for are a decrease in postvoid residual volumes, increased uroflow rates, and normalization of EMG patterns. Effective treatment also helps control the secondary complications of reflux, UTIs, and in extreme cases, urinary tract deterioration.

NOCTURNAL ENURESIS

One of the most common urologic complaints in children is nocturnal enuresis (NE). Most children achieve nighttime continence by the age of 5. The significance of NE is dependent on the patient's age, the parents' and child's expectations, and his or her social situation.

Our understanding of the pathophysiology of NE has progressed greatly in recent years, and the disorder is now understood to be heterogeneous and genetically complex in nature. Abnormalities in nocturnal urine production, bladder reservoir function, arousability, molecular genetics, or a combination of these may be responsible for nighttime wetting. This new understanding of NE has had enormous impact on both the diagnosis and treatment of the disorder. Nevertheless, much is left to learn and many controversies still remain.

DEFINITIONS

In accordance with the International Children's Continence Society recommendations, the term *primary nocturnal enuresis* is used to describe bedwetting in a child who has never had a dry period of longer than 6 months. A child with *secondary NE* is one that wets the bed but had previously been dry for at least 6 months prior.[33] *Monosymptomatic nocturnal enuresis* (MNE) describes bedwetting in children with no daytime urinary symptoms to suggest an underlying voiding dysfunction. *Nonmonosymptomatic or primary nocturnal enuresis* (PNE) is used to describe NE associated with bladder overactivity.[34]

EPIDEMIOLOGY

The overall prevalence of NE declines with age. By the age of 4 years, it is estimated that 20%–25% of children frequently wet the bed. This decreases to 5%–10% by the age of 7.[35–38] Fourteen percent of children between the ages of 5 and 9 years and 16% between 10 and 19 years will stop wetting the bed annually.[39] In this longitudinal cohort study, 92% of 1129 children born in 1 year were followed for 6 years with primary enuresis remission rates of approximately 15% per year.[39]

Although spontaneous cure occurs throughout childhood and adolescence, the problem may persist in 0.5%–3% of the adult population.[40–43]

Although PNE is more common in young boys, by adolescence the incidence in males is equivalent to that in females.[44] The prevalence of NE is similar throughout the world.

PSYCHOLOGICAL IMPACT

Primary NE may have a profound psychological and social impact on both the child and his or her family. Enuresis may affect a child's normal activities and development. This, in turn, may affect the child's family.[45–47] There is some controversy regarding how enuresis affects self-esteem. A recent review concluded that there is no evidence that bedwetting leads to lower self-esteem.[47] Conversely, some studies have shown that children with NE have worse self-esteem and significantly more behavioral and psychological problems, including anxiety, depression, aggressiveness, and attention deficit, when compared with normal age-matched nonenuretic patients.[45–47] After a successful cure, abnormal behavioral and psychological problems have been shown to improve in some studies, possibly indicating that the problems are a result of the NE and not vice versa.[46,48,49] Surely, attaining dryness will not negatively impact a child's self-esteem. The child's age itself may change his or her attitude toward enuresis. Butler reported that younger children focus on the immediate consequences of enuresis, whereas older children are more likely affected by the social and emotional aspects of the condition.[50] Interestingly, comorbid psychiatric disorders can be found in up to 75% of secondary nocturnal enuretics.[51,52] At least 46% of parents have some concern with regards to NE, while 17% worried a great deal.[53,54]

In a study by Haque et al., the mean anticipated age of dryness according to parents was 3.18 years. When asked for possible causes for their child's NE, parents believed that emotional problems (35.5%), heavy sleeping (38.2%), physical problems (21.4%), familial problems (28.9%), and small bladders (10.7%) may be responsible.[55]

NE may also lead to punishment. Some mothers believe that their child is wetting on purpose and choose not to treat their children and may even punish them.[54] The reported rates of punishment in the 1980s were 37% in the United Kingdom and 35.8% in the United States.

ETIOLOGY

Family studies have repeatedly demonstrated high rates of relatives affected by enuresis. The risk for a child to be enuretic is 40% if one parent and 70% if both parents had been enuretic.[56] Early studies reported that 32% of fathers and 23.9% of mothers of children with enuresis were enuretic as children.[57]

Based on twin studies, the most common mode of transmission is autosomal dominant with high (90%) penetrance.[58] Additionally, about 45% of patients with NE were found to have an autosomal dominant mode of inheritance.[59] Linkage analyses have been used in the study of NE, and several loci have been identified; however, there is no clear association of any of the loci with any particular type of enuresis.[60,61]

PATHOPHYSIOLOGY OF NOCTURNAL ENURESIS

One or more of several pathophysiological mechanisms may cause NE.

Nocturnal Polyuria

In classic studies, Rittig and colleagues and Norgaard et al. demonstrated abnormalities in the circadian rhythm of antidiuretic hormone (ADH) secretion in bedwetters.[62–64] In these patients, urine production during sleep exceeds bladder capacity.[62,64,65] Children with NE associated with nocturnal polyuria will often wet in large quantities soon after going to sleep.[66,67] However, nocturnal urine production may vary considerably from night to night, and urine volume is significantly larger on wet nights compared with dry nights in enuretics.[68] Therefore, nocturnal polyuria is best evaluated during nights when enuresis is experienced.[69]

Based on the abnormalities in diurnal ADH production, desmopressin (dDAVP) was introduced for the treatment of PNE. Response rates using desmopressin of approximately 70% have been reported by various studies.[64,70] Other factors that may also contribute to excessive nocturnal urine production are currently being investigated. These include an increase in the nocturnal

release of other hormones that regulate solute excretion, e.g., angiotensin II, aldosterone, and atrial natriuretic peptide. Abnormalities of renal function may also contribute to PNE. A study examining renal function in enuretic children found decreases in free water and solute reabsorption in the thick ascending limb of Henle's loop.[71] Hypercalciuria, prostaglandin production, aquaporin 2 (AQP2) dysfunction, and sleep apnea may also play a role in the pathophysiology of NE.[71–74]

Nocturnal urine production is approximately 50% of daytime production in early childhood.[75] This decrease in urine production is controlled by decreases in free water excretion secondary to nocturnal increases in the release of ADH and/or decreases in solute excretion related to the release of angiotensin II and aldosterone.[76,77]

Children with NE and increased nocturnal urine output generally have normal functional bladder capacity and a favorable response to treatment with desmopressin.[78]

Impairment in Sleep Arousal Response

Problems with arousal must exist in order for a child to wet his or her bed. Enuretic children have been shown to have poor arousability in response to acoustic stimuli, and specific brainstem dysfunction has been suggested.[79,80] In Wolfish's study, acoustic stimuli of up to 120 dB were successful in waking 39.7% of the control group and only 9.3% of enuretic patients. Enuretic male patients have also been found to be more difficult to arouse than age-matched controls.

Bladder Dysfunction

Small functional bladder capacity and detrusor overactivity may play an important role in the pathophysiology of NE.[69,81–84] Despite normal daytime voiding, approximately 30% of enuretic patients studied with simultaneous sleep electroencephalogram and cystometric monitoring were found to have detrusor instability while sleeping at night.[85] In studies by Yeung et al. and Oredsson and Jorgensen, a majority of enuretic patients with symptoms refractory to treatment were found to have a small functional bladder capacity.[69,83] When the results of cystometric studies obtained during the daytime were compared with those obtained during sleep, enuretic patients were categorized into two groups: (1) those with normal urodynamics and bladder capacity during daytime and marked detrusor instability, diminished nocturnal functional bladder capacity, and small volume voiding only after sleep at night, and (2) those with abnormal daytime urodynamics associated with various types of occult underlying bladder dysfunctions and significantly reduced functional bladder capacity and small volume voids, both day and night.[83,84] Additionally, up to 70% of adult patients with persistent PNE have been found to have detrusor instability and reduced functional bladder capacity.[86]

The incidence of significant anatomical and functional bladder abnormalities is low in primary MNE; however, patients with severe, treatment-resistant enuresis and *adults with new-onset* NE may have an underlying abnormality that should be thoroughly investigated.[83,84,87]

EVALUATION

In order to properly manage a child with primary NE, it is first necessary to determine possible causes for the condition. Is the bedwetting a result of nocturnal polyuria (increased nocturnal urine production during sleep), or is it due to a reduction in nocturnal functional bladder capacity? Although a good voiding history may illicit these occult abnormalities, it is often after a failed course of desmopressin that the clinician becomes suspicious that nocturnal polyuria may not be the cause. The initial recommendation for these children is limiting fluid and solute intake in the evening, void before bedtime and have the parents take the child to void before they go to bed. If this does not work, nocturnal enuretics will often improve with desmopressin alone or in combination with an anticholoinergic agent and/or enuretic alarm therapy.

To avoid a delay in effective treatment, patients should have a detailed history and physical examination. A voiding diary is often useful. Occasionally, ultrasonography, uroflow, and even urodynamic studies may be indicated.

HISTORY

A careful history should include questions to help determine whether the enuresis is primary or secondary. The number and time at which nighttime wetting occurs should be noted. Every effort should be made to rule out the possibility of an underlying voiding dysfunction. Questions regarding daytime incontinence, urgency, frequency, posturing, infrequent voiding, and difficulties voiding should be asked. Additionally, questions not directly related to voiding, including questions regarding fluid intake, sleep habits, bowel habits, and clumsiness, should be asked.

The answers to such questions may be useful in helping to determine whether the NE is due to nocturnal polyuria or a diminished functional capacity. With careful questioning, daytime voiding symptoms may be elicited, helping to successfully structure a treatment plan for bothersome NE. Optimally, a structured, validated questionnaire should be used.

Voiding Diary or Frequency Volume Chart

It is difficult for most parents and children to precisely answer questions regarding the number of episodes of NE per week, urinary frequency, and voided volumes. Hence, a voiding diary or frequency volume chart is extremely useful. Despite day-to-day variation, a voiding diary is an important tool in helping to determine the etiology of the NE, devising a treatment plan, and monitoring response to treatment. Optimally, a voiding diary should include record of a child's fluid intake and urine output. The frequency and volume voided should also be recorded. Attempts should be made to quantify the amount of urine voided during the enuretic episode. Although somewhat controversial, the functional bladder capacity is assumed to be the volume of the largest single void that occurs overnight.[88]

After analyzing various studies, Hjalmas and colleagues recommend a 2-day, 3-night voiding record.[65,88,89] As volumes of urine produced and storage capacity may vary from day to day, Hjalmas and colleagues suggest that a uroflow with measurements of postvoid residual may be helpful to screen for dysfunction voiding.[88]

In children with secondary enuresis, a social and psychological history becomes important. Various factors may affect a child's voiding habits, including the family situation, the school environment, and other changes in the child's daily way of life. It is very important to discuss the family's response to the child's enuresis. Children may feel punished by having to wear a pull-up. They may be ridiculed by siblings and other family members, worsening the child's social situation.[88]

When children have extended periods of dryness, they should be congratulated by both their parents and the professionals caring for them. Not only does the child feel better for not wetting, but also it becomes apparent to him or her that this is a condition he or she may outgrow. Parents may become reassured that anatomic problems are unlikely to be the cause of the enuresis.

A thorough sleep history should be taken, and it should be noted how much the child is sleeping compared with other children his or her age.[90] Obstructive sleep apnea may contribute to the child's NE. Parents should be asked if the child snores, is a mouth breather, or has restless sleep. Teachers may have noted morning tiredness.

NONMONOSYMPTOMATIC NOCTURNAL ENURESIS

Hjalmas and colleagues describe complex bedwetting as nonmonosymptomatic bedwetting.[88] These are children whose NE is refractory to therapy or those that are noted to have anatomical or neurological abnormalities. Here the challenge remains that of identifying urological causes for the wetting. As previously described, this search is often aided by a thorough history. If dysfunction storage or voiding is identified, the cause for the refractory nighttime wetting may become treatable.

Further evaluations, including uroflow examinations, urodynamics, and radiographic evaluation of the upper tracts, often become necessary. The signs and symptoms of dysfunctional voiding were previously described in this chapter.

PHYSICAL EXAMINATION

Anatomical and behavioral causes for enuresis may be ruled out by a thorough physical examination. From the moment a child enters the examination room, his or her behavior and gait should be noted. Possible signs of neuropathic voiding dysfunction include abnormal gait, spinal deformities, and foot abnormalities, including asymmetry, high-arched feet, or hammertoes. *Physical signs of occult spinal abnormalities, such as dimples, tufts of hair, skin discoloration, lipoma, asymmetrical buttocks, and gluteal clefts, are also important.* Anal sphincter tone and perineal sensation and reflexes should be checked.

The abdomen is then palpated to evaluate a distended bladder and stool. If stool is palpated, the possibility of dysfunctional elimination syndrome should be considered.[91]

In *boys,* a genital examination may reveal an abnormal meatus, e.g., stenotic, hypospadiac, or epispadiac. The significance of these meatal abnormalities may vary and can often be elicited when a voiding history is obtained. If the significance of the anomalies remains unclear, a more objective uroflow may be obtained.

Abnormalities of the female perineum that may contribute to abnormal voiding include labial adhesions, urogenital sinuses, ectopic ureteral orifices, and hypospadiac urethra. Some of these conditions may be related to dysfunctional voiding in girls.[92] Both girls and boys should be carefully examined for signs of sexual abuse.[93,94]

Laboratory Tests

For a healthy child with MNE, laboratory tests rarely contribute to the evaluation and treatment of the condition. A urinalysis and urine culture may be considered to screen for UTI, diabetes mellitus, and diabetes insipidus.

Urodynamics and Imaging

Urodynamic evaluation and upper tract imaging are necessary where there is a suspicion of neurological dysfunction or in a severely refractory patient.

TREATMENT

Only after carefully reviewing the child's history and physical examination can a sound treatment plan be devised. It is imperative to answer these two questions before treating the patient: (1) Is an underlying voiding dysfunction present? (2) Is bedwetting the only complaint? (Is this truly MNE?) If the condition is truly MNE, does the child have increased nocturnal urine production (nocturnal polyuria) or a small functional bladder capacity?

It is argued that treatment of enuresis should be based on its etiology.[66,95] The treatment plan should be tailored to the individual child's needs.

Starting Out

Prior to initiating therapy with an alarm or a medication, the clinician should review some basic guidelines with the child and his or her parents. It has been shown that educating them about the problem will help compliance and outcome of therapy.[96] These guidelines include encouraging regular daytime voiding schedules, avoiding the intake of excessive food or fluid intake for several hours before bed, emptying the bladder before bedtime, and encouraging the child to get adequate amounts of sleep for age.[88,90] A low-calcium and low-sodium dietary content of the afternoon and evening meals may also be useful.[73,97] Some parents find it useful to arouse and escort the child to the bathroom before they themselves are going to sleep.

Additional motivational tools, such as having children mark a calendar to signify wet and dry nights, have had some success. The literature has reported success in up to 18% of children utilizing such tools.[98]

Comorbid conditions, such as encopresis, constipation, and psychiatric disorders, should be treated at this point in time as well. Up to 72% of enuresis has been cured with treatment of these comorbid conditions.[99,100] If present, daytime voiding symptoms should be treated prior to initiating therapy for NE.[101,102]

For treatment of enuresis to be successful, the child and family must be motivated and the clinician must be prepared to be patient and supportive. Expectations should be realistic, and relapses should not be considered complete failure. If a child does not consider wetting a problem, the outcome of therapy may be poor and waiting may be more appropriate. Children younger than 6 years old are rarely interested in becoming dry at night. Wetting should not be punished, and successes should be rewarded.

The condition may be treated using these simple guidelines alone. It is our practice to provide baseline counseling prior to the initiation of specific treatment in most enuretic children.

Alarm Therapy

Currently available enuretic alarms are small devices that are clipped to the undergarments and worn throughout the night or placed at the bedside. Alarms worn on the body are as effective as bedside alarms.[103] Although highly effective, the exact mechanism by which alarm treatment works is not known. The behavioral modification is not classical conditioning, as the stimulus is a result of the behavior. Instead, the alarm appears to work by negative reinforcement or avoidance. It goes off and awakens the child during voiding; the child then must get out of bed and finish voiding in the toilet or hold his or her urine until later.

Alarm therapy is a successful treatment for bedwetting with initial and long-term success rates of 70%–90% and 50%–70%, respectively.[104,105]

Evidence-based medicine teaches us that alarm therapy is among the most effective interventions for treating childhood NE. Several systematic reviews and meta-analyses report success rates of 65%–70%, with a treatment duration of 5–12 weeks, and stated relapse rates of 15%–30% in the 6 months after treatment.[106–108] As efficacy improves with time, enuresis alarms may not be suitable in families unwilling to wait several months for improvement.[109]

A Cochrane review was recently published on alarm interventions, including 22 randomized controlled trials involving 1125 children.[109] After considering 952 potentially relevant studies, only 22 were considered of quality sufficient to be analyzed. Therefore, although highly successful in certain situations, the review concluded that studies comparing alarms with pharmaceuticals are warranted.

Expectations and commitment to the alarm's use must be discussed, as alarm therapy requires a motivated child and family, and significant effort and time. The alarm may interrupt not only the affected child's sleep but also that of the parents and other siblings. Once the alarm is activated, a parent will often have to wake up and get out of bed to assist the child to the bathroom to finish voiding, change the sheets and pajamas, return the child to bed, and reset the alarm. Often, the child is not fully awake during this entire process. The parent, on the other hand, is fully awake, and unless he or she is fully committed to the cause, he or she may begin to resent the child, leading to parental intolerance.[110] Parental intolerance may lead to discontinuation or early withdrawal from alarm treatment.[111]

When using the alarm, biweekly follow-up has been suggested to monitor therapy and continue motivation.[88] The alarm should be used for at least 1 month after a period of sustained dryness. Twenty-nine to sixty-six percent of children may relapse; however, this does not preclude repeated use of the alarm.

Use of the alarm may affect arousal, overnight urine production, and nocturnal bladder capacity. Oredsson and Jorgensen reported increase of bladder capacity but no change in nocturnal urine output or vasopressin secretion.[69]

Butler has defined outcomes to aid in the evaluation of the effectiveness of alarm treatment: *initial success*, a minimum of 14 consecutive dry nights within 16 weeks of alarm treatment; *relapse*, two wet nights in 2 weeks; *continued success*, no relapse within 6 months of initial success; and *complete success*, no relapse within 2 years of initial success.[112]

Alarm treatment is widely believed to be the most effective therapy for NE with the best long-term results.[113] In the metanalysis by Houts et al., 62% of children were dry at the end of treatment, with 47% dry at follow-up.[114] Similar successes with up to 77.9% dry have also been reported, with the likelihood for 14 consecutive dry nights 13.3 times higher than that without treatment.[100] Successes using the alarm are also considered to be more durable by some, as treatment using desmopressin and tricyclics has not been sustained once therapy has been withdrawn.[109] However, *long-term* desmopressin treatment has also been shown to produce sustained improvement, although reported cure rates with alarm are generally higher.[115,116]

Predictors of poor response with the enuresis alarm have been summarized by Butler and Stenberg 95 and Hjalmas et al. and include parental intolerance and annoyance, children with low self-esteem, behavioral problems or lack of motivation, family history of bedwetting, associated daytime wetting, lack of supervision, inconsistent use, family stress, psychiatric disorder in the child, failure to awaken in response to the alarm, unsatisfactory housing conditions, and more than one wetting episode per night.[88,105,111,117–120]

PHARMACOLOGICAL TREATMENT

Desmopressin (dDAVP)

Many patients with MNE lack the nocturnal rise of ADH, therefore causing an imbalance in the normal circadian variation in urine production. This results in the production of large quantities of dilute urine at night. When the amount of urine produced overnight exceeds the bladder capacity, NE will occur.[121] A study by Hansen and

Jorgensen confirmed that nighttime urine production was reduced during desmopressin treatment.[122]

Arginine vasopressin (also known as ADH) is a polypeptide produced in the hypothalamus and released from the pituitary gland. Its release is due to hyperosmolality or a low effective circulating blood volume. The polypeptide's effect is on V2 receptors of the collecting ducts and distal tubules to enhance water reabsorption.[123] It is also a potent vasopressor, through independent actions on V1 receptors.

Desmopressin is an analogue of vasopressin. Unlike ADH, this analogue has increased antidiuretic activity without vasopressor activity. The half-life is 1.5–3.5 hours. Desmopressin is commercially available in an oral and intranasal formula. The usual dose is 0.2–0.6 mg orally or 10–40 μg intranasally at bedtime with immediate clinical effects. Fluid intake should be limited when the drug is used. A simple suggestion is to avoid drinking for 2 hours before bed and to limit fluid intake to 8 ounces after dinner.

Desmopressin is regarded safe for use in children and is generally well tolerated with a low incidence of adverse events.[115,116] Continued safety has been demonstrated with long-term use. Klauber reported no serious adverse reactions in 516 cases.[124] In the SWEET study, only 6 of 242 children (2.5%) withdrew during the long-term intranasal treatment due to very mild adverse events. All monitored clinical and laboratory parameters remained within normal in this study.[115]

The risk of water intoxication should be discussed with parents prior to initiating dDAVP therapy, and it is for these reasons that fluid intake during dinner and before bedtime should be limited. In this case, hyponatremia is due to a large amount of fluid intake while taking the drug.[125]

Although children with nocturnal polyuria and low nocturnal urine osmolality should respond best to dDAVP treatment, some studies have not found any significant differences in urine output, osmolality, or vasopressin secretion in responders and nonresponders.[126,127]

Prior to labeling a child as a nonresponder, it is important to know whether the medication has been administered correctly. In children who do not respond to treatment with dDAVP, nocturnal hypercalciuria and hypernatriuria should also be considered.[73,97]

Other predictors of good response to desmopressin therapy include larger bladder capacities,[88] older children,[128,129] fewer wet nights at presentation,[128,130] normal functional bladder capacity,[127,129] primary as opposed to secondary NE,[131] only one wet episode during the night, enuresis that occurs during the first 2 hours of sleep,[127] a family history of NE,[132,133] and initial good response to the smallest dose of desmopressin used in the study (20 μg intranasally).[134]

Several controlled studies have demonstrated the effectiveness of desmopressin in the treatment of NE,[135–138] regardless of the route of administration. Positive response (defined as more than a 50% reduction of wet nights) has been reported in 60%–70% of patients.[64,70,65] A review of randomized trials comparing desmopressin to placebo found that desmopressin was significantly better in 13 of the 14 studies.[70] Based on the Cochrane report by Glazener and Evans, patients treated with dDAVP were 4.6 times more likely to achieve 14 consecutive dry nights than those treated with placebo.[139] With a more selected population of children with primary NE, Caione et al. found a 79% success rate after the administration of desmopressin.[140]

When dDAVP treatment is successful, the drug should be stopped for 1 week every 3 months to evaluate whether the problem has been corrected. The annual cure rate in children that have been treated with dDAVP is approximately 30%.[115] Permanent cure may increase to 74.5% by gradually discontinuing the drug and positively reinforcing dry nights over a 10-week period.[141]

Unfortunately, relapse after the cessation of treatment is common, and long-term treatment may yield a better response. Of 399 enuretic children recruited in the Swedish Enuresis Trial,[115] 61% responded to desmopressin treatment initially, and of those responders, 61% were dry after 1 year of treatment. However, using an intent-to-treat analysis, only 19% of patients remained dry after the cessation of therapy.[115]

Desmopressin may be helpful in children who have failed alarm therapy or in families where motivation to use the alarm is lacking. In the short term, desmopressin is reported to produce more rapid improvement than alarm therapy. As children who do poorly with the alarm may do well with dDAVP, the converse may also be true.

Oxybutinin

The antimuscarinic agent oxybutynin is often used as part of combination therapy in enuretic children with a small bladder capacity, daytime incontinence, or detrusor overactivity. Oxybutynin should not be the first recommended therapy for a child with MNE. Yeung et al. found that 30% or more of enuretic children refractory to therapy had detrusor overactivity at night.[84] When using oxybutynin, bladder training should also be considered, as in unselected populations of children with NE, oxybutynin has not been effective in randomized controlled studies.[142] Watanabe and Kawauchi[143] reported a 67% success rate with oxybutynin in a group of children with bladder instability as a cause of their NE; Kass et al.[144] reported a 90% success rate. The drug is also indicated in children with day- and nighttime incontinence and dDAVP nonresponders. The efficacy may improve when combined with desmopressin.[145,146]

Tricyclic Antidepressants

Tricyclic antidepressants, such as imipramine, were extensively used in the treatment of enuresis in the 1970s and 1980s. Imipramine has fallen out of favor for several reasons, including cardiotoxic side effects, risk of death with overdose, and its psychopharmacological properties. The mechanism of action for this drug in the treatment of NE is unclear, although it may act by reducing detrusor activity and increasing bladder capacity secondary to anticholinergic and smooth muscle relaxant effects. Additionally, it may enhance arousal and suppress REM sleep or decrease urine production by a stimulating vasopressin release.[147,148]

Due to the lower efficacy and more dangerous side effect profile of this drug compared with desmopressin

(only 17% of children who were dry during treatment with imipramine remained dry 6 months after cessation of medication and alarm treatment), it should only be used when all else has failed. Due to its dangerous nature, it may be wise to have the treatment be followed by a physician with experience using the drug.[115]

OTHER THERAPIES

Combination Therapy

Some children with NE may have more than one cause for their condition. The most common combined cause of NE is lack of Anti-diuretic hormone (ADH) with poor arousability. In these children, combined therapy may be more successful than a single therapy alone.

Studies using combined desmopressin and the enuresis alarm on unselected groups of children have been published. In a study by Bradbury and Meadow, 71 children were randomized to alarm plus desmopressin (40 μg) or alarm monotherapy for 6 weeks.[149] The combined therapy was more effective than the alarm alone, particularly where the child had severe NE and behavioral problems. In a study by Sukhai et al.,[150] with a crossover design, children were randomized into two treatment groups, i.e., alarm plus desmopressin or alarm with placebo. The results suggested that alarm plus desmopressin was better ($p = 0.05$) than alarm with placebo in treating NE. In a double-blind placebo-controlled study, Leebeek-Groenewegen et al.[151] examined 93 children with MNE. Children were treated with alarm plus desmopressin or alarm plus placebo for 9 weeks. Based on the results of this study, the authors concluded that desmopressin does not result in higher cure rates, and that combined treatment is not justified in all enuretic children at the outset of treatment.

For children with enuresis associated with bladder overactivity, a combination of bladder training and anticholinergic therapy yields success rates of 67%–100%.[85,113,146] Combination therapy with oxybutynin and desmopressin has also been found to be effective in this subgroup of patients.[140]

Behavioral Therapies

Houts suggested that the addition of selected behavioral procedures produces better outcomes than alarm monotherapy.[152] These behavioral procedures include arousal training, normalized voiding, and dry-bed training. *Arousal training* involves reinforced waking and toileting in response to the alarm's trigger. *Normalized voiding* encourages children to increase their fluid intake and participate in timed voiding during the daytime in an attempt to increase cognitive control over voiding. *Dry-bed training* uses the enuresis alarm. The child takes responsibility for removing wet sheets and remaking the bed and also has two waking schedules to ease arousability from sleep.[153] However, in a study by Bollard and Nettelbeck,[154] it was found that the enuresis alarm accounted for most of the success achieved through dry-bed training.

Alternative Therapies

Numerous studies using traditional Chinese acupuncture and laser acupuncture for the treatment of NE have been published.[155,156] In a prospective randomized study comparing laser acupuncture with desmopressin in patients with nocturnal polyuria, laser acupuncture was found to be as efficacious as desmopressin.[156]

Treatment for Nonresponders

Absorptive nocturnal hypercalciuria may be responsible for NE in some children that remain nonresponders despite therapy with dDAVP and anticholinergics. Pace et al. demonstrated that enuretic patients with hypercalciuria that failed to respond to dDAVP became desmopressin responders once they were treated with a low-calcium diet.[157]

Abnormalities in AQP2 urinary excretion have recently been reported as another possible cause of NE.[73] Urinary AQP2 and hypercalciuria correlated with the severity of enuresis in children. The association between AQP2 and hypercalciuria was further strengthened in a recent study by Valenti et al.[158] After 6 months of combined treatment with desmopressin and a low-calcium diet, enuresis resolved in 80% of patients. Arginine vasopressin levels returned to normal, hypercalciuria resolved, and day/night AQP2 ratios returned near normal levels. Based on these recent report, Hjalmas and colleagues suggest that "it may become mandatory to study the CaU/CrU ratio to determine if the enuretic patient is hypercalciuric or not, as a first step to a correct therapeutic strategy for nocturnal enuresis."[115]

CONCLUSION

Despite advances in our understanding of NE, the condition remains complex. The key to success involves a motivated patient and family.

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CHAPTER 55

Constipation and Lower Urinary Tract Symptoms

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INTRODUCTION

Constipation is a common childhood problem and is thus frequently encountered by pediatric urologists, particularly given the common embryological origin, location, and innervation of the gastrointestinal and genitourinary tracts. This chapter reviews criteria, prevalence, and treatments for constipation and provides an evidence-based review of its relationship with lower urinary tract symptoms (LUTSs) and urinary tract infections (UTIs). In bulleted lists, a summary of evidence is shown, with details about the supporting studies included below the summary for each section.

CRITERIA FOR THE DIAGNOSIS OF CONSTIPATION

- Rome II, Rome III, and Paris Consensus on Childhood Constipation Terminology (PACCT) diagnostic criteria (Table 55.1) are the most commonly used.
- Rome III and PACCT criteria are less restrictive than Rome II criteria.
- Ninety-five percent of children would have met diagnostic criteria for constipation without rectal exam in one study.
- The Bristol Stool Form Scale (BSFS) has not been validated as a tool to diagnose constipation in children.
- Radiographic studies alone, including abdominal radiograph and pelvic ultrasound (US), do not reliably distinguish constipated and nonconstipated children.

Diagnostic Criteria

The International Children's Continence Society (ICCS) provided guidelines for the diagnosis of constipation in children with LUTSs in 2006.[1] They recommended use of either Rome II criteria or the PACCT Group criteria (Table 55.1). Rome II criteria were established by expert consensus, modeled after a similar meeting by experts in Rome, 7 years prior, to establish adult gastrointestinal terminology (Rome I). However, Rome II criteria are often considered too restrictive, and experts convening in Paris at the Second World Congress of Pediatric Gastroenterology, Hepatology and Nutrition in 2004 formed an alternative definition of chronic constipation, referred to as PACCT chronic constipation. In 2006, Rome II criteria to diagnose constipation in children and adolescents were modified by expert opinion and literature review into Rome III criteria.[2]

Studies have compared the various definitions for "functional constipation" (symptoms not explained by structural or biochemical abnormalities). A longitudinal prospective study of 128 children referred to a tertiary clinic for symptoms of chronic constipation was performed, evaluating children based on Rome II and PACCT criteria.[3] The children had a mean age of 5.6 years (standard deviation [SD] 3.8) and 62 (48%) were boys. The authors found functional constipation according to Rome II criteria in 60 (48%) versus in 112 (89%) using PACCT criteria ($p = 0.001$), with poor agreement between the two sets of criteria (kappa = 0.173), implying that these two sets of criteria identify different groups of patients. Most children had symptoms of straining with defecation of scybalous stools (80%) and painful defecation (66%).

A study comparing Rome II and Rome III criteria found that more patients met criteria for functional constipation using Rome III criteria.[4] Retrospective chart review of 336 consecutive patients referred to a tertiary clinic for symptoms of constipation (mean age 6.4 years, SD 3.5 years, 61% boys) revealed constipation by Rome II criteria in 34% versus 87% with Rome III criteria ($p < 0.0001$). While all patients in this report underwent rectal exam for palpable fecal mass, the authors noted that 95% of patients met criteria for functional constipation without the rectal exam. The authors concluded that Rome III criteria were less restrictive than Rome II criteria for functional defecation disorders (symptoms not explained by structural or biochemical abnormalities).

Indicators for Gastroenterology Referral

In addition to the diagnostic criteria for constipation, pediatric urology providers should be aware of "red flags" on history and physical exam, listed in Table 55.2, that can apply to children with constipation and should prompt referral to gastroenterology.

TABLE 55.1 Diagnostic criteria for functional constipation

	Rome II[51]	Rome III[2]	PACCT[52]
Age	Infant to 16 years	Developmental age of ≥4 years	Not specified
Duration of symptoms	Not specified	≥2 months	≥8 weeks
No. of symptoms/exam findings to meet criteria	At least 2	At least 2	At least 2
Diagnostic criteria	1. Majority of stools scybalous, pebble-like, hard 2. Firm stools ≤2 times/week 3. No metabolic, endocrine, structural disease	1. ≤2 defecations per week 2. At least 1 episode of fecal incontinence per week 3. Stool retentive posturing 4. Hard or painful bowel movements 5. Large-diameter stools that could obstruct the toilet 6. Large fecal mass in rectum	1. <3 defecations per week 2. >1 episode of fecal incontinence per week 3. Large fecal mass in rectum or palpable in abdomen 4. Large-diameter stools that could obstruct the toilet 5. Stool retentive posturing 6. Hard or painful bowel movements

TABLE 55.2 Findings on history and/or physical exam in children with constipation that should prompt referral to gastroenterology

Constipation red flags	
History	**Physical**
Failure to thrive	Absent/brisk lower limb reflexes
Delayed passage of meconium >24 hours	Mouth ulcers
Abnormal bowel habits since birth	Blood/mucous mixed with stool
Sensitive to cold, fatigue, dry skin, pallor	Perianal skin tags or fistulas
Change in bowel pattern with cow's milk	Associated hypotonia
Weight loss	Tight empty rectum
Vomiting	Pilonidal dimple covered by a tuft of hair

Source: Adapted from Lewis SJ, Heaton KW. *Scand J Gastroenterol* 1997;32(9):920–4.

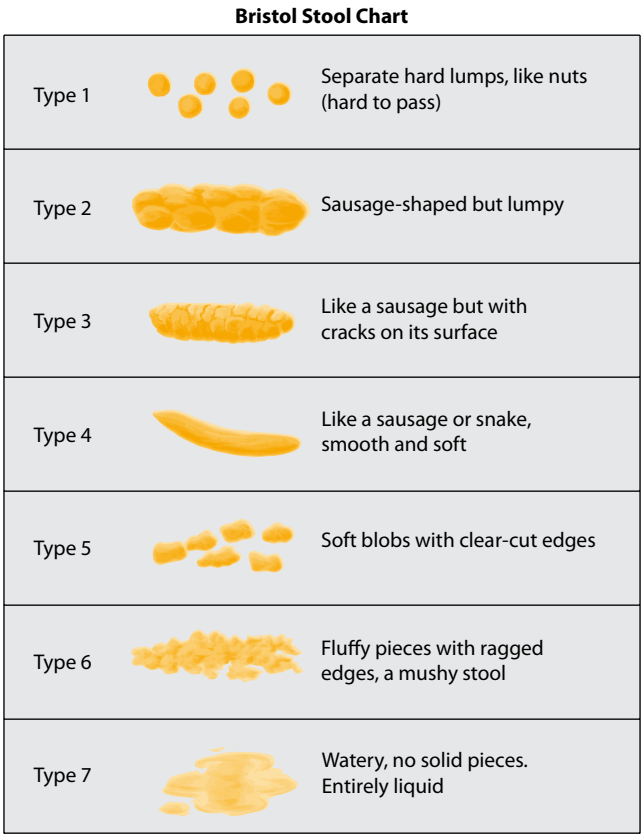

FIGURE 55.1 The Bristol stool scale source, this form is now owned by the ROME foundation. (Adapted from Lewis SJ, Heaton KW. *Scand J Gastroenterol* 1997;32(9):920–4.)

Bristol Stool Form Scale

Although many authors use stool Type 1 (separate hard lumps, like nuts, hard to pass) and Type 2 (sausage shaped but lumpy) as a diagnostic proxy for constipation, the Bristol stool form scale (BSFS) (Figure 55.1) was originally validated to measure gastrointestinal transit time in adults and is not specific for the diagnosis of functional constipation.[6,7] In addition to being nonvalidated to diagnose functional constipation, the BSFS has not been validated for use in children. The only study validating a stool form scale for use in children was published in 2011 and used a modified version of the BSFS.[8] The authors shortened the scale to five categories instead of seven, omitting Type 3 (like a sausage or snake but with cracks on its surface) and Type 5 (soft blobs with clear-cut edges) in order to decrease the amount of discrimination that must be made by children while maintaining a range of stool forms. A total of 310 children aged 3–18 years were shown 10 standardized pictures of stool (2 pictures per category, previously shown to have high interrater agreement among 14 pediatric gastroenterologists).[9] Initial testing by showing the scale without reading the descriptors aloud showed low reliability among the first 119 children for children of <8 years (intraclass correlation coefficients 0.16, 0.61, 0.72, 0.81, and 0.86 for ages 3–5 years, 6–7, 8–10, 11–13, and 14–18, respectively). Patients aged ≥8 years correctly rated the stool pictures >78% of the time. The descriptors were then read aloud

for the subsequent 191 patients, which improved reliability for children aged 6–7 years (intraclass correlation 0.74), with >80% ratings correct for children of ≥6 years old, leading the authors to conclude that the scale is valid and reliable for children of >6 years with descriptors read aloud and children of >8 years without descriptors read aloud. Now that a stool form scale has been validated for use in children, it can be applied to children meeting Rome III and/or PACCT diagnostic criteria to determine if Type 1 and Type 2 stool indeed reflect functional constipation, as has been commonly attributed in the literature. It remains to be seen whether the scale is valid for multiple ratings across time in children.

Abdominal Radiograph

Multiple radiographic fecal load scoring tools exist to diagnose constipation, which are nicely reviewed by Reuchlin-Vroklage et al.[10] This review points out the subjective nature of most of these grading systems and demonstrates that there is high intra- and interobserver variability in these studies, questioning the utility of abdominal radiography as a reliable diagnostic tool. The synthesis of evidence in this review showed that radiographically defined constipation was equally present in clinically constipated and nonconstipated children. Furthermore, these x-ray studies have only been used to diagnose constipation and have not been validated to see whether score changes reflect symptoms over time and/or with therapy. One retrospective study evaluated the variability among pediatric urology providers grading constipation using three commonly accepted grading scales: Barr, Blethyn, and Leech.[11] The abdominal radiographs of 80 children aged 4–12 years were separately reviewed in random order by six providers, including two experienced pediatric urologists (17 and 20 years), a pediatric radiologist with 20 years' experience, and three pediatric nurse practitioners with variable experience (2–10 years). Interrater reliability (the agreement between raters) using kappa statistics (where kappa values of >0.75 indicate excellent, 0.4–0.75 good, and <0.4 poor reliability) was poor to marginally good using all three rating systems: Barr 0.049–0.481, Blethyn 0.045–0.451, and Leech 0.119–0.273. Similarly, intraclass correlations (another measure of reliability testing describing the reproducibility of measurements made by different observers rating the same image measured with a scale similar to kappa statistics) were quite poor for all three rating systems (Barr 0.026, Blethyn 0.201, and Leech 0.331). None of the scoring systems provided reliable results between observers in grading constipation.

Ultrasound

Recently, abdominal and pelvic US has been evaluated as a means of diagnosing constipation. Four case-control studies have been performed to evaluate the transverse diameter of the rectum on US as a diagnostic tool for constipation.[12–15] In total, 265 children with constipation (various definitions) and 237 controls were evaluated by measuring the transverse diameter of the rectal ampulla approximately 1–2 cm above the symphysis, with the bladder moderately full, with angles varying from 15° from the transverse plain to 90° to the abdominal wall, with the largest diameter recorded in three studies and the mean of three values in one.[15] All four studies found significantly larger mean and median rectal diameters among patients with constipation compared with controls; however, there was substantial overlap between constipated patients and controls in two of the three studies.[12,13] Furthermore, rectal diameter was found to increase with age in both constipated children and controls,[12,14] such that a cutoff value to diagnose constipation has not been proposed. In one study of 51 children (27 with Rome III constipation and 24 without, average age 9.1 years, SD 2.7), a cutoff determined by the mean of healthy controls + 2 SD (3.34 mm) would misclassify 13/51 (25%) children if used as the only diagnostic criteria for constipation.[15] A similar cutoff for constipation (3.00 mm) in another study of 95 constipated children versus 82 controls (median age 5.5 years, intraquartile range 3.75) would also misclassify 25% of children in both groups.[12] Given the subjective nature of US evaluation, it has been recommended that inter- and intrarater reliability, validity, and objectivity are determined prior to adopting US as a mainstay diagnostic tool to diagnose constipation, particularly since it is unknown if the diameter changes in relation to the timing of the last defecation.[14]

PREVALENCE

- Constipation, defined by <3 bowel movements per week, is present in approximately 10% of children (range 1%–30%).
- In five epidemiologic studies, constipation was equally prevalent in boys and girls, whereas in two studies, girls had a higher prevalence.

TABLE 55.3 Normal frequency of bowel movements in infants and children

Age	Bowel movements per week (mean ± 2 SD)	Mean number of bowel movements per day
0–3 months breastfed	5–40	2.9
0–3 months formula fed	5–28	2.0
6–12 months	5–28	1.8
1–3 years	4–21	1.4
>3 years	3–14	1.0

Source: Adapted from Fontana M et al. *Acta Paediatr Scand* 1987;78:682.

- Fecal soiling is present in ≤10% of children and is more commonly reported in boys.

Table 55.3 depicts the normal bowel habits based on a population-based sample of 662 healthy Italian children, endorsed by the Constipation Subcommittee of the Clinical Guidelines Committee of the North American Society for Pediatric Gastroenterology and Nutrition.[16]

Population-based epidemiologic studies of both urinary and bowel habits among healthy children are scarce. Approximately 10% of children aged 0–18 years have <3 bowel movements per week according to a 2006 systematic review of 18 epidemiologic studies (range 0.7–29.6%, intraquartile range of average bowel movements per week 1.3–21.3).[18] The wide variation was thought to be attributable to various definitions of constipation, as well as differing durations of symptoms for inclusion. Of the seven studies reporting gender-specific prevalence, boys and girls had an equal prevalence of constipation in five, whereas two reported a higher prevalence in girls. Additional relevant studies not included in the aforementioned systematic review are listed below.

1. A questionnaire-based study of parents of 16,516 Korean school children aged 5–13 years demonstrated the following symptoms in the 3 months prior to the survey: decreased stool frequency (<3 times/week) in 1103 (6.7%), painful or difficult defecation in 2609 (15.8%), Bristol stool Type 1 or 2 in 1941 (11.8%), and fecal incontinence in 1293 (7.8%). Parents of girls were more likely to report decreased frequency, painful defecation, and constipation on the Bristol scale, whereas parents of boys reported fecal incontinence more often (9.8% boys vs. 5.8% girls).[19]
2. A cross-sectional study of 5282 Japanese school children (mean 9 years, range 7–12), found constipation (<3 times/week, duration not specified) in 971 (18%).[20]
3. Constipation defined by Rome II criteria was present in 5.7% of 2856 Australian children (mean 7.3 years, SD 1.3) whose parents answered a validated questionnaire about bowel and bladder habits. Fecal soiling was present in 10%.[21]
4. A cross-sectional school-based study of 1694 Turkish children (49% boys, 9.2 ± 1.2 years) demonstrated constipation defined by PACCT criteria in 6.9% and fecal incontinence in 3.1%.[22]
5. Healthy children from kindergarten and elementary schools were invited to participate in a study about voiding and defecation function, with 778 participants (53% boys, 7 ± 2 years). Constipation (<3 times/week) was present in 85 (11%); BSFS Types 1 and 2 were present in the past month in 213 (28%) children. There was no difference between genders.[23]
6. In a retrospective chart review, constipation defined by PACCT criteria was present at some point in the child's life in 109 (23%) of 482 children followed in a primary care clinic, including 55 (22%) boys and 54 (23%) girls ($p = 0.9$). The mean age at first visit for constipation was 4.9 years, ranging from <1 in 14 (13%) to 12–14 years in 6 (6%) of the 109 patients. Fecal soiling was documented in the charts of 4.4% of patients, with more boys than girls affected by fecal soiling (7% vs. 1%, $p < 0.001$).[24]

RELATIONSHIP WITH URINARY SYMPTOMS

LUTSs for Daytime Urinary Incontinence: Summary of Evidence

- Constipation was not associated with overactive bladder (OAB) symptoms in three population-based studies and one randomized controlled trial (RCT); it was marginally associated with frequent voiding ± urgency in one population-based study.
- Fecal incontinence was associated with OAB symptoms in two population-based survey studies.
- One study showed slightly increased postvoid residual (PVR) and decreased voiding efficiency and percent children with a PVR of >20 mL in those with <3 bowel movements a week, but no difference in voided volumes, uroflow patterns, urinary urgency, or daytime incontinence.
- One study in children with refractory LUTSs demonstrated no predictable urodynamic (UD) changes when UD was performed with and without pressure-controlled rectal filling.

A questionnaire-based study of parents of 16,516 Korean school children aged 5–13 years defined OAB by ICCS guidelines as urgency with or without urge incontinence. OAB was present in 2740 children (16.6%), which decreased with age from 22.9% at age 5 years to 12.2% at 13 years ($p = 0.0001$).[25] Constipation, as defined by Bristol scale Types 1 and 2, present in 1941 (11.8%) children, was marginally associated with OAB on multivariate analysis ($p = 0.045$, odds ratio [OR] and confidence interval [CI] not provided), but constipation defined by a frequency of <3 times/week and painful defecation was not. Fecal incontinence also increased risk ($p = 0.0001$, OR and CI not provided).

Among the 5282 Japanese school children reported above, constipation was defined as <3 bowel movements per week, and OAB was defined as ≥1 SD beyond the average number of voids per day per age ± urge incontinence at least one time per month.[20] OAB was equally present in children with and without constipation (20% with vs. 18% without, $p > 0.05$). Polysymptomatic enuresis (OAB + nocturnal enuresis) was slightly more common in children with constipation (3% with vs. 2% without, $p < 0.05$).

A population-based survey of 580 Brazilian children (47% boys, 6.1 ± 2 years) that administered a modified Farhat validated voiding dysfunction scale found urinary urgency in 50%, with voiding dysfunction (defined by >6 points for girls, >9 points for boys) present in 23%.[49] Straining to defecate in the past 15 days occurred in 8.8%. Constipation, defined by >72-hour intervals between bowel movements, was present in only 3.1% and was not associated with dysfunctional voiding on the questionnaire.

Healthy children from kindergarten and elementary schools were invited to participate in a study about voiding and defecation function, including uroflow and US-measured PVRs.[23] Among 778 participants (53% boys, 7 ± 2 years) with eligible data, results were reported for children with constipation (<3 times/week), present in 85 (11%). Patients with low defecation frequency had higher PVRs than those without (9.0 mL vs. 5.9 mL, $p = 0.01$), decreased voiding efficiency (93% vs. 95% of expected bladder capacity [Age + 2] × 30 mL, $p = 0.04$), and a higher percentage with PVR > 20 mL (18% vs. 7%, $p = 0.01$). There were no differences in percent with non-bell-shaped curves (19% vs. 14%, $p = 0.32$). Responses to questions regarding urinary urgency ($p = 0.93$), daytime urinary incontinence ($p = 0.53$), or fecal incontinence ($p = 0.62$) were similar between groups, and there was no correlation between urinary urgency and defecation frequency (Pearson $R = 0.06$). There were no differences in PVR, voiding efficiency, percent elevated PVR, or flow patterns between patients with and without constipation defined by BSFS Types 1 and 2, present in 213 (28%) children.

An analysis of fecal load by abdominal radiograph in one RCT found no association of urinary urge symptoms with constipation defined by the Leech and Blethyn abdominal radiograph rating systems.[26] A total of 138 children (62% girls, 7.3 ± 2.3 years) underwent baseline urinary and bowel symptom questionnaires and abdominal radiograph, of whom 61 (47%) had radiographically defined constipation using either scale. Fecal load scores as judged by a pediatric radiologist blinded to treatment group had no correlation with OAB or fecal symptoms at baseline or after 1 month of therapy (Spearman's correlation $R = -0.155$, $p = 0.08$ baseline, and $R = -0.149$, $p = 0.28$ posttherapy). Fecal load scores before and after treatment with polyethylene glycol (PEG) or placebo did not change, yet 45% of children in both groups had improvement in OAB symptoms, including complete response in five patients taking placebo and six patients taking PEG.

A prospective study by Loening-Baucke of 234 children (75% boys, 9 ± 3 years) referred for both constipation (not defined) and fecal soiling showed incontinence at least one time per week in 46% (duration not defined), including nocturnal enuresis in 17%, daytime and night wetting in 17%, and daytime wetting in 12%.[27]

In a prospective study, 26 consecutive children undergoing urodynamics (UD) for severe LUTSs were evaluated by gastroenterology specialists for constipation.[28] Of these, 20 (77%) meet Rome III criteria for constipation, while 6 did not. Clinical symptoms and UD findings were not different between these groups, including median bladder capacity (percent estimated), voiding pressures, median flow rate, peak flow rate, and PVR estimates. UD study was performed with and without inflation of a barostat pressure-controlled balloon, with no predictable change in UD patterns when the rectum was balloon filled.

A retrospective chart review of 482 children (51% boys, 8.6 ± 3.9 years) seen in a primary care office in Iowa demonstrated that 109 (22.6%) had been evaluated for constipation (PACCT criteria) at some point in their life.[24] Fecal incontinence was documented in 4.4%. Daytime urinary incontinence (≥1 time/week at any point after age 5 years, duration not specified) was recorded in the charts of 9.1% of 389 children (selection criteria not specified) in whom constipation was documented versus 3.9% in whom constipation was not documented; however, the author does not address whether urinary symptoms were routinely recorded as part of the review of systems in children presenting with constipation versus all patients.

Retrospective chart review of 40 patients referred with complaints of urinary urgency, frequency, and/or incontinence revealed constipation by Rome III criteria in 45% and BSFS Types 1 and 2 in 30%. Fecal soiling occurred in 12.5% (Kim 2011).

Nocturnal Enuresis: Summary of Evidence

- Three cross-sectional studies reported that constipation was not a risk factor for nocturnal enuresis.
- Two stated that fecal incontinence was associated with enuresis, found in 11% of enuretics in one study.

Among the 2856 Australian children in the cross-sectional study described above, enuresis was categorized as mild (1–6 episodes in the past month), moderate (≥7 episodes in past month), and severe (nightly the past 1 month).[21] Constipation, defined by ROME II criteria, was not associated with nocturnal enuresis (mild OR 0.7 [95% CI 0.4–1.2], moderate OR 1.5 [95% CI 0.7–3.6], and severe OR 0.7 [95% CI 0.3–1.9]). However, fecal incontinence was an independent risk factor for enuresis in multivariate logistic regression adjusting for age (mild OR 1.6 [95% CI 1.0–2.4], moderate OR 2.1 [95% CI 1.1–4.3], and severe OR 2.7 [95% CI 1.6–4.4]).

A survey study of 5350 children (mean 9.1 years, SD 2.9) demonstrated enuresis ≥2 times/week in 679 (12.7%).[29] Constipation (defined as <3 bowel movements per week for at least 6 months) was present in 48/679 (7.1%) enuretic children versus 68/4671 (1.5%) without nocturnal enuresis ($p < 0.0001$). However, it was not specified how daytime urinary symptoms were assessed, and logistic regression controlling for factors such as age and gender was not performed.

Among the 5282 Japanese school children reported above, monosymptomatic nocturnal enuresis was equally present in children with (3.0%) and without (3.6%) constipation (<3 times/week, $p > 0.05$).[20]

Among the 1694 Turkish children (49% boys, 9.2 ± 1.2 years) reported above, enuresis (≥2 nights/week) was present in 108 (6.4%).[22] While constipation defined by PACCT criteria was associated with enuresis in univariate analysis, it was not a significant predictor on multivariate analysis (OR 0.88, 95% CI 0.19–4.20). However, fecal incontinence was a risk factor for enuresis on multivariate analysis (OR 6.13, 95% CI 1.46–4.83). Fecal incontinence was present in 17 (11%) children with enuresis versus 35 (2%) without. This study did not differentiate patients with mono- or polysymptomatic enuresis, with 64% and 36% of enuretic children reporting urination >5 times/day and history of UTI, respectively.

A prospective study of 277 children (66% males, mean 8.6 years) referred for nocturnal enuresis (unclear if mono- or polysymptomatic) reported fecal soiling in 125 (45%), bowel movements <1 time/day in 114 (41%), straining to defecate in 158 (57%), and hard stools in 62 (22%).[30] The

clinician reported that 100 (36%) children were constipated based on a compilation of these symptoms, whereas only 39 (14%) children were identified as constipated by parental response on a (nonvalidated) questionnaire.

A retrospective chart review of 482 children (51% boys, 8.6 ± 3.9 years) seen in a primary care office in the study detailed above found nocturnal enuresis occurring ≥1 time/week in 5.4% of a subset of 389 children (selection criteria not specified, duration of incontinence not specified), including 13% of children meeting PACCT criteria for constipation and 3% of children without constipation.[27]

UTI and VUR: Summary of Evidence

- In one series, 11% of constipated patients had a history of UTI and 2% had vesicoureteral reflux (VUR).
- One case-control study demonstrated that encopresis was more likely in patients with >1 vs. 1 UTI.

Of 234 consecutive children (75% boys, 9 ± 3 years) referred for chronic constipation (not defined), UTIs were present in 25 (10.7%, including 6/176 boys and 19/58 girls).[27] A total of four (1.7%) patients (one male, three females) had VUR on voiding cystourethrography, which was obtained in all children with UTIs or any unexplained fever. No additional UTIs were noted during a follow-up of at least 12 months in these children who were treated with disimpaction, maintenance laxatives (typically milk of magnesia), and antibiotic prophylaxis until constipation resolved.

A retrospective review of 94 children aged 2–14 years demonstrated moderate to severe fecal load via the Blethyn grading system (Grade 2 or 3) in 7/33 (21%) controls, 9/24 (38%) with 1 UTI, 12/24 (50%) with 2–5 UTIs, and 7/13 (54%) with >5 UTIs.[31] However, reading of the abdominal radiographs was not blinded, and there was unequal gender distribution among the groups, with females comprising nearly all the patients with two or more UTIs compared with a substantial portion of males with 0 or 1 UTI.

A case-control study compared dysfunctional voiding rates among children with and without febrile UTI who presented to the emergency room with fever between 0 and 2 years of age by mailing Dysfunctional Voiding Symptom Score (DVSS) questionnaires to them several years later, after the age of toilet training (mean age 7 years).[32] Among 248 children (123 with a history of UTI in infancy and 125 controls), 13% had to push or had pain with defecation >50% of the time, and 64 (26%) had encopresis defined by the DVSS questionnaire. They found an overall rate of dysfunctional elimination syndrome (DES) in 53/248 (21%) children, with no difference between children with and without febrile UTI in infancy (22% vs. 21%, $p = 0.82$). Among the 115 children with UTI in infancy, 18% of children with VUR (diagnosed at the time of their original UTI) and 25% without VUR had DES symptoms after toilet training ($p = 0.52$). VUR was not associated with DES on univariate or multivariate analysis. Of these 115, 31 children had one or more confirmed additional UTIs. Univariate analysis demonstrated that encopresis and VUR were seen in a higher percentage of patients with >1 versus 1 UTI, while DES (DVSS score >6 for girls and >9 for boys and present in 11 [36%]) was not (OR 2.2, 95% CI 0.99–5). Multivariate analysis demonstrated that encopresis was the only significant risk factor for UTI recurrence (OR not given, $p = 0.03$).

Therapy for Constipation: Summary of Evidence

Does therapy for constipation impact LUTSs of daytime urinary incontinence?

- Two RCTs showed LUTSs improved irrespective of the presence or absence of constipation at follow-up.

Several nonrandomized uncontrolled studies report urinary symptom improvement with the use of laxatives; however, given a high placebo response rate for urologic symptoms (approximately 40% based on a Cochrane meta-analysis of patients receiving placebo for OAB), uncontrolled studies are unable to address whether therapy directed specifically toward constipation offers additional benefit beyond placebo.[33]

To our knowledge, only one RCT has evaluated the use of a laxative on symptoms of OAB without additional bladder therapy, such as timed voiding or anticholinergics.[26] A total of 138 children (85 [62%] girls, mean age 7.3 years, SD 2.3) underwent baseline urinary symptom questionnaires (modified DVSS) and were randomized to daily PEG (mean 0.5 mg/kg/day) or placebo in this double-blind study. Symptom questionnaires were repeated after 1 month, with improvement defined as ≥20% decrease in urge symptoms (≥3-point decrease on a 16-point scale). The randomization process, power calculation, and primary outcome variables were specified, and patients and providers were blinded to the treatment group; however, the study had a high dropout rate, with 71/138 (51.4%) completing the study per protocol. Demographics were similar for the study noncompleters and completers, and five of six patients able to be contacted by phone said that they did not follow up due to symptom improvement. Patients in both groups showed significant improvement in urinary symptoms (pre- and posturine scores: 13.9/10.5 for placebo and 13.9/10.2 for PEG, $p < 0.0001$ for both), with 17/38 (44.7%) and 16/33 (48.5%) assigned placebo and PEG, respectively, showing symptom improvement. PEG did not demonstrate an added benefit over placebo in intention-to-treat ($p = 0.77$) or per-protocol ($p = 0.84$) analyses. Two patients assigned PEG and one assigned placebo developed diarrhea as the only adverse events.

A multicenter, prospective RCT (European Bladder Dysfunction Study) evaluated urinary and bowel symptoms at baseline and after 6 months of treatment.[50] Of the 179 enrolled children (89% girls), 17 (9%) had <3 bowel movements per week and/or painful defecation, and 57 (32%) had fecal soiling. After therapy (biofeedback, placebo, or oxybutinin), fecal soiling decreased to 38/179 (21%, $p = 0.035$), with no difference in the three treatment arms. However, children with resolution of their fecal soiling and/or constipation had outcomes for their urinary incontinence similar to those with persistent fecal soiling and/or constipation, leading the authors to conclude that disordered defecation does not cause urinary incontinence, and that both conditions improve with demystification and behavioral training.

In the Loening-Baucke study mentioned above, urinary incontinence was present at least one time per week in 107 (46%) of 234 children (75% boys, 9 ± 3 years) referred for both constipation and fecal soiling.[27] At a mean follow-up of 15 months, daytime incontinence was cured (not defined) in 47 (73%) of 64 children, and nighttime wetting was cured (not defined) in 39 (49%) of 80 children who had wetting episodes at baseline at least one time per week (some patients had both day and night wetting; thus, the total number of patients does not total 107). After ≥12 months of therapy, patients were considered cured of constipation when >3 bowel movements per week without soiling was achieved without the need for laxatives, which was achieved in 121 (52%). Incontinence decreased significantly in patients both with and without cure of their constipation.

Does therapy for constipation impact nocturnal enuresis?

- No RCTs using laxatives or other bowel regimens as monotherapy for monosymptomatic nocturnal enuresis have been performed
- Two studies showed nocturnal enuresis improved with constipation therapy.

In a prospective study, 234 patients with functional constipation and encopresis, mean age 9 years (SD 3), were evaluated for urinary incontinence one or more times per week at baseline and at least 12 months after therapy, which consisted of disimpaction and maintenance with milk of magnesia, mineral oil, or sorbitol, plus high-fiber diet and behavioral therapy.[27] Nocturnal enuresis was present in 80 (34%) children, equally split between patients with and without daytime incontinence. With a mean follow-up of 15 months, nocturnal enuresis resolved in 39 patients, including 26 (63%) whose constipation resolved and 13 (33%) who had continued constipation (<3 bowel movements per week and/or fecal soiling off laxatives) ($p < 0.05$). Results were not substratified by those with and without daytime incontinence.

A retrospective review of 30 consecutive patients, mean age 9 years (5–15), with a "chief complaint of nocturnal enuresis" found that 10% reported constipation (bowel movement less than every other day).[34] Using a novel measurement of the ratio of the widest point of the rectal diameter to the pelvic outlet diameter on abdominal radiograph, all children had "fecal rectal distention" therapy with PEG for ≥2 weeks and the enuresis was cured in 25 (83%). The indications for radiography and number of wet nights per week before bowel therapy were not stated, and it was unclear if these patients had daytime incontinence.

Does therapy for constipation impact UTI or VUR?

- There are no RCTs using laxatives or other bowel regimens as monotherapy in patients with recurrent UTIs.
- There are no RCTs using laxatives or other bowel regimens as monotherapy for VUR.

CONSTIPATION TREATMENT

Behavioral Therapy

Behavioral treatment is the mainstay in relieving anxiety surrounding toileting issues for both the families and the patient and begins with education of the diagnosis. It is important to convey that fecal soiling is usually involuntary and a result of constipation, and a child should not be punished for the soiling. The goal for each child should be one or two soft bowel movements without straining daily. The Bristol stool scale has typically been used as a visual reference tool to evaluate treatment success. A 4 or 5 on this scale should be the goal daily without straining or discomfort.

Behavior recommendations typically include a regular toileting routine, such as sitting to have a bowel movement for 5–10 minutes approximately 30 minutes after breakfast, lunch, and dinner to prevent stool withholding. Parents should be counseled about correct toilet posture and provide support under the child's feet with stooling to decrease straining. Some advocate a reward system, such as stickers placed on a calendar, with a reward after success during a defined time interval.[35]

Biofeedback can be used in patients who show pelvic floor dysfunction (prolonged and excessive straining) and poor response to traditional laxative therapy. The therapist helps the patient learn how to relax the pelvic floor musculature and the external anal sphincter rather than straining to produce a bowel movement.[36] The frequency of therapy varies from program to program. However, a 2011 meta-analysis showed no evidence that biofeedback training added benefit to conventional therapy in managing pediatric fecal incontinence.[37] However, behavioral interventions plus laxative therapy showed decreased soiling at 3 and 12 months in one small trial (OR 0.14, 95% CI 0.04–0.51, and OR 0.20, 95% CI 0.06–0.65, respectively).

Diet

Families should be encouraged to increase daily consumption of fresh fruits, vegetables, whole-wheat, and whole-grain products in their diet and limit processed foods that are constipating. Some children benefit from a brief trial of withholding cow's milk.[38] One study showed that dried plums (prunes) resulted in improvement in the number of bowel movements per week (primary outcome) and stool consistency scores compared with psyllium in 40 adults with chronic constipation.[39]

Fiber

Dietary intake of fiber using the following equation is recommended to decrease constipation: grams of fiber/day = age in years + 5 g.[40] Systematic review of six RCTs of dietary fiber compared with placebo in adults with chronic idiopathic constipation demonstrated improvement in the following: global symptoms (86.5% vs. 47%), straining (56% vs. 29%), increased mean number of stools per week (3.8 vs. 2.9), and decreased pain with defecation.[41]

Probiotics

Probiotics have recently gained in popularity for the treatment of constipation and irritable bowel–related conditions. While meta-analysis has recently shown probiotics to have a protective effect on antibiotic-induced diarrhea in children, research has not come to a firm conclusion

TABLE 55.4 Osmotic laxatives

Osmotic agents	
Mechanism of action: Increases stool frequency and loosens stool	
Side effect: Abdominal pain, diarrhea, electrolyte disturbance	
Oral PEG	0.26–1 g/kg/day maintenance 1–1.5 g/kg/day for 3 days (disimpaction)
Oral lactulose	5 mL bid (1–5 years) 10 mL bid (6–10 years) 15 mL bid (11–18 years) 1–3 mL/kg divided twice daily (disimpaction)
Oral magnesium hydroxide	5–10 mL daily (3–12 years) 25–50 mL (13–18 years) 1–3 mL/kg/day of 400 mg/5 mL for 3 days (disimpaction)
Oral magnesium citrate	100–150 mL/day (6–12 years) disimpaction 150–300 mL/day (>12 years) disimpaction
Rectal glycerin suppository	1 infant suppository per rectum (<6 years) 1 adult suppository per rectum (> 6 years)

Source: Adapted from NASPGHAN Constipation Guideline Committee. *J Pediatr Gastroenterol Nutr* 2006;43(3):e1–13.

for use in pediatric constipation.[42] One crossover, double-blind study of 59 children (range 5–15 years) treated with goat yogurt or goat yogurt supplemented with 10^9*Bifidobacterium longum* showed improvement in defecation frequency and abdominal pain in both groups, with additional improvement in the *B. longum*–supplemented group.[43] A prospective randomized double-blind controlled trial in 159 children with constipation (<3 bowel movements per week) treated with a dairy product containing 10^9 *Bifidobacterium lactis* versus a control product showed significant improvement in stool frequency in both groups, with no difference between groups.[44]

Laxative Therapy

When dietary and behavioral interventions fail to improve symptoms of constipation, laxative therapy is often considered. The immediate concern may be disimpaction, followed by maintenance therapy (Tables 55.4 and 55.5) for long-term management to prevent reaccumulation of feces. Typically, the maintenance course is 3–6 months, after which symptoms should be reevaluated. When performing disimpaction and titrating medications, frequent follow-up should be performed. Children who do not respond to initial treatment strategies or continue to have trouble with fecal soiling with a maintenance regimen should be evaluated by a pediatric gastroenterology specialist.

Osmotic Agents

These agents increase water in the intestinal lumen to increase frequency and consistency.[45] PEG, lactulose, Kristalose®, glycerin suppositories, and magnesium hydroxide are examples of osmotic laxatives (Table 55.4). Side effects include electrolyte disturbance, diarrhea, and abdominal pain. Increasing fluid intake with these medications to prevent electrolyte imbalance is important, particularly when using these agents for disimpaction. Clinically, it is often recommended to mix or take

TABLE 55.5 Bulking, stimulant, and lubricant laxatives

Agent	Mechanism of action	Therapeutic effect	Dose	Side effects
Psyllium husk	Bulking agent	Increases stool frequency and improves consistency	0.85–1.7 g once daily to tid (<6 years) 1.7 g daily to tid (6–11 years) 3.4 g daily to tid (>12 years)	Gas, bloating
Senna	Stimulant laxative	Stimulation of nerve endings in colonic mucosa	Dosage form (8.6 mg tablet) ½–1 tablet once daily (2–6 years) 1–2 tablet daily or bid (6–12 years) 2 tablets daily (>12 years)	Abdominal pain, diarrhea
Mineral oil	Lubricant	Lubricates and softens stool	15–30 mL/year of age up to 240 mL daily for disimpaction Maintenance 1–3 mL/kg/day Not recommended for infants of <1 year of age	Lipoid pneumonia if aspirated, staining of undergarments, abdominal cramps

Source: Adapted from NASPGHAN Constipation Guideline Committee. *J Pediatr Gastroenterol Nutr* 2006;43(3):e1–13.

medication with an electrolyte replacement solution, such as Gatorade®.

PEG has been extensively studied and is used frequently due to ease of dosing, accessibility, palatability, and effectiveness. A Cochrane review of 1643 children from 18 RCTs reports that PEG increases the number of stools per week compared with placebo, and it appears to be superior to placebo, lactulose, and milk of magnesia in terms of effect and/or adverse events, but the authors also recommend interpreting the results with caution due to poor study quality and significant risk of bias due to lack of blinding and selective reporting.[46] PEG appears to be well tolerated with minimal adverse effects in the short term.

Bulking Agents

Bulking agents can be used for occasional constipation as an initial treatment option (Table 55.5). They are readily available over the counter for a low cost and are available in multiple forms (powder, tablet, cracker, etc.). Psyllium husk (Metamucil®) has been shown in adults to help retain fluid in the stool and increase fecal mass to improve the frequency and consistency of bowel movements. Other similar agents containing calcium polycarbophil (Fibercon®) have the same mechanism of action; however, research shows an unknown positive value of therapeutic effect. *Bulking agents may be particularly beneficial to the patient with both constipation and diarrhea by addressing both symptoms*. The bulking tends to reduce the soiling related to diarrhea while helping to soften the stool and increase stool mass. To reduce uncomfortable side effects, such as gas and bloating, increasing the dose slowly is helpful.

STIMULANT AND LUBRICATION LAXATIVES

Stimulant laxatives such as senna and bisacodyl (Senokot® and ExLax®) may be used for occasional constipation (Table 55.5). These agents are thought to act on the enteric nervous system by stimulating nerve endings in the colonic mucosa and inhibiting water absorption to create a bowel movement.[45] The therapeutic effect of stimulant laxatives is typically 8–12 hours.[47] Side effects include abdominal pain, diarrhea, and electrolyte disturbance. *Chronic use of stimulant laxatives may cause permanent injury to the enteric nervous system*.[45]

Lubricants such as mineral oil may also be used to produce a bowel movement. They can be used for disimpaction or daily to soften stool. Side effects observed in infant populations, such as aspiration pneumonia, must be considered (Table 55.5). Mineral oil also appears to be well tolerated and effective in a meta-analysis of two studies of 287 patients.[46]

Enemas

Enemas are typically used for disimpaction. Phosphate enemas at a dose of 6 mL/kg up to 135 mL in children 6 years and older can be used.[48] This therapy is highly successful and should be used where clinically relevant, but it can cause fear and discomfort for a child. When appropriate, a lubricant or stimulant laxative may be preferable over an enema for disimpaction.

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CHAPTER
56

Operations for the Weak Bladder Outlet

Anthony J. Casale

INTRODUCTION

Surgery to correct urinary incontinence began in 1852 with a procedure to divert the ureters into the sigmoid colon of a boy with exstrophy.[1] Our understanding of the physiology and cause of urinary incontinence has grown slowly over the past century, and more has been learned in the past 25 years than in prior medical history. Early surgeons did not have the necessary technology to define the physiology of the bladder neck, but they were keen observers of anatomy. As early as 1906, the German surgeon Trendelenburg had suggested dividing the symphysis pubis to gain access for surgical narrowing of the bladder outlet in epispadias patients with the goal of improving urinary control.[2] Hugh Hampton Young was the first American urologist to identify the abnormal anatomy of the bladder neck as the cause of the patient's urinary incontinence and devise surgery to correct it in 1908. In 1919, Young presented his original procedure to provide continence in patients with bladder outlet incompetence.[3]

By examining these patients with early cystoscopes and at the time of open surgery, Young noted that the bladder neck and proximal urethra were enlarged and funnel shaped. The remainder of the bladder appeared healthy. He surmised that if he could restore the bladder neck and proximal urethra to a more normal appearance, then function would improve. He excised a wedge of mucosa from the posterior urethra and bladder below the trigone and narrowed the muscle with a single layer of sutures.

Since Young's bold procedure, surgery for the weak bladder outlet has progressed from the goal of re-creating normal anatomy to that of constructing continence mechanisms that bear no resemblance to the normal bladder outlet. Other developments in urinary tract reconstruction, such as intermittent catheterization, bladder augmentation, and continent catheterizable stomas, have made new procedures to repair the weak bladder outlet possible and offer solutions to problems that early surgeons saw as incurable.

After decades of becoming bolder in our approach to the bladder neck, the last few years have seen a realization of the limitations of reconstructive surgery to the bladder outlet and a turn to less aggressive and disruptive bladder surgery. A better understanding of the physiology of the bladder and stresses on the bladder outlet has led to a more selective approach to increasing bladder outlet resistance. Increased awareness of long-term negative consequences of altered anatomy and physiology has led surgeons to aspire to alter the bladder outlet anatomy only enough to achieve the desired result of socially acceptable continence.

INDICATIONS AND EVALUATION

Urinary incontinence may be the result of bladder outlet inadequacy in conditions such as epispadias, exstrophy, cloacal exstrophy, traumatic injuries of the urethra and bladder neck, urogenital sinus, bilateral ectopic ureters, and neurologic conditions. Indications for bladder outlet surgery in these conditions include evidence that weakness of the outlet is a cause of incontinence and the failure of maximal medical therapy to correct the problem.

The bladder outlet includes the bladder neck and proximal urethra; together, they may be considered a unit and normally function as a sphincter in both boys and girls. There is no identifiable anatomic sphincter, but a mixture of smooth and striated muscle, intracellular matrix, and mucosal factors that combine to make up a functional sphincter.[4] Compression of the urethral lumen and the resultant outlet resistance depends on several factors. Among the components that make up the normal sphincter mechanism are smooth and striated muscle tone and contractions, elastic properties of the urethra, mechanical forces transmitted from the abdomen, and structural support of the posterior urethral wall and bladder neck against which the urethra is compressed with increased abdominal pressure. The conditions that cause incontinence in children often present inadequacies in several, if not all, of these components.

In health, the bladder neck provides a variable resistance to the flow of urine through the urethra. The resistance is stable when the bladder pressure is low and increases as the pressure rises with bladder filling. It also increases reflexively with increased bladder pressure due to coughing or Valsalva's maneuver, and it decreases dramatically when the patient begins to void. For the bladder neck to maintain continence, it must be able to generate pressure within the lumen that is greater than the pressure within the bladder at all times except during voiding.

There are several methods to evaluate the competency of the bladder outlet. Just as Young noted, the cystoscopic appearance of the bladder neck reflects its function. When viewing from the proximal urethra, the posterior lip of the bladder neck should be elevated above the level of the

urethra and the base of the bladder. The bladder neck should close easily when fluid flow through the cystoscope is stopped. Although these observations are helpful, they are by no means completely reliable in predicting continence.

The bladder outlet may also be evaluated by imaging with a radiographic cystogram. A competent bladder outlet appears closed as the bladder is filled, and contrast should not leak into the urethra. The incompetent bladder outlet may remain open and funnel shaped during the filling process or may open with Valsalva's maneuver or suprapubic pressure (Figure 56.1).[5] Lateral views of the cystogram may reveal the lack of adequate elevation and suspension of the posterior bladder outlet.

Urodynamic studies of the bladder are important in determining causes of incontinence. Bladder leak point pressure and sphincter electromyography (EMG) are commonly used to measure bladder neck function. Leak point pressure is simply the pressure within the bladder at which fluid begins to leak through the bladder outlet into the urethra. Sphincter EMG is the measurement of electrical activity of the striated muscle of the sphincter. The sphincter EMG is most helpful in evaluating coordination of the detrusor and sphincter and may be of some benefit to document neural innervation of the sphincter in incontinent children. It is seldom helpful in children who are candidates for bladder outlet surgery.

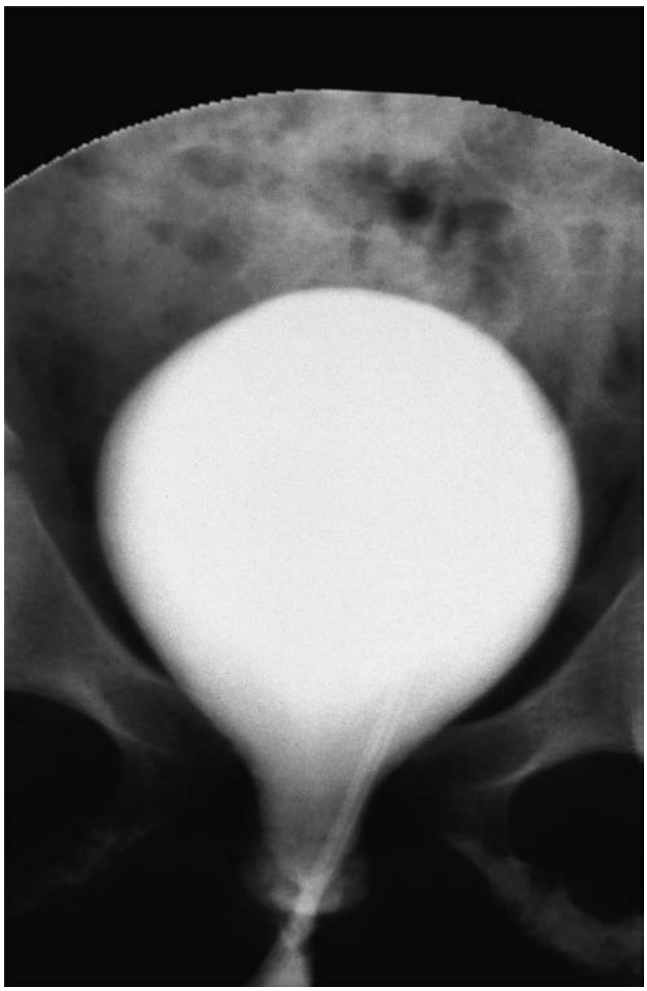

FIGURE 56.1 Voiding cystourethrogram of a patient with an open bladder neck during filling with contrast. The bladder neck is funneled during the entire study.

On the other hand, bladder leak point pressure is the most reliable objective study in incontinent children due to bladder outlet dysfunction. Low leak point pressures indicate incompetence of the bladder outlet and may cause incontinence independent of detrusor function. McGuire et al. defined the importance of leak point pressure in children with myelodysplasia and neuropathic bladder when they found that high leak point pressures of >40 cmH_2O resulted in upper tract deterioration due to reflux and hydronephrosis.[6] Children with pressures of <40 cmH_2O were protected from such changes but were prone to leak urine easily owing to weak bladder outlet. They also found that the radiographic appearance of an open bladder neck did not correlate well with measured leak point pressures.

McGuire found that children with myelomeningocele have fixed bladder outlet resistance that is located distal to the bladder neck and does not vary with filling or leaking. When these children were treated with intermittent catheterization and anticholinergic medications, patients with closed bladder necks on cystogram were uniformly continent, whereas only 60% of those with an open bladder neck became continent. This finding was independent of leak point pressure, indicating its limits in predicting continence in all patients.

Leak point pressure should be measured with a small urethral catheter (5 or 7 Fr). The water should be infused with a pump rather than by gravity. The technique should be standardized for each measurement, since Decter and Harpster have demonstrated that measured values of leak point pressures in children vary with catheter size and with rate and method of infusion.[7]

Patients should be encouraged to cough and sit or stand if possible to measure leak point pressures in a dynamic, more normal, setting. The volume at which leaking occurs is important because it reflects the functional capacity of the bladder and prognosis for continence.

Other urodynamic measurements are critical in diagnosing the cause of incontinence. Bladder pressures and volumes indicate the storage capacity of the bladder and must be adequate for continence. Compliance may be considered the inverse of stiffness and is a helpful indicator of bladder adaptability. Poorly compliant bladders tend to produce higher pressures with lower volumes of urine, making patients more prone to upper tract deterioration and incontinence.[8]

Detrusor measurements in children with completely incompetent bladder necks may be performed by inflating the balloon of a Foley catheter at the bladder neck and pulling it down to occlude the bladder outlet.[9] It is fruitless to consider treatment of bladder outlet incompetence unless the bladder itself has adequate volume and pressure characteristics for the storage of urine.

When evaluating incontinent children as candidates for bladder outlet surgery, a voiding or catheterizing diary can yield invaluable and practical information. Unlike radiographic and urodynamic examinations, these diaries represent the level of incontinence during normal activity. Some parameters, such as functional storage capacity of

the bladder, may be quite different from values that hospital tests may imply. We have patients measure voided or catheterized amounts of urine obtained, the times that the bladder is emptied, when incontinence occurs, the degree of incontinence, and activities associated with leaking. This information, along with urodynamic data, examination by cystogram, and cystoscopy, may be needed to define the cause or causes of incontinence.

If incontinence is due to incompetence of the bladder outlet, the physician has two basic treatments available, medical and surgical. Medical treatment must always be exhausted completely before considering surgery. This is important not only because some patients will become dry with medical management alone, but also because medical regimens requiring family and patient participation may demonstrate that the family is committed and willing to comply with similar catheterization and medicine schedules that necessarily accompany most surgical procedures to create continence. If the family can give medication and catheterize the child prior to surgery, it is likely that they will do so after bladder outlet surgery.

MEDICAL THERAPY

Children found to have inadequate bladder outlet resistance may be treated with various nonsurgical modalities. Some therapy helpful in incontinent adults has no role in children. Pelvic floor exercises, biofeedback, and electric stimulation of the bladder outlet have not been helpful in children with incontinence who suffer from anatomic and neuropathic conditions.

There are medications that have been effectively used to stimulate muscles of the weak bladder outlet. They include α-sympathomimetic agents such as ephedrine and ephedrine-like compounds that stimulate the large number of α-adrenergic receptor sites found in the proximal urethra and bladder neck and cause smooth muscle contraction.[10] These compounds produce troublesome side effects in some patients, such as hypertension, anxiety, and palpitations. Results have not been reliable in this group of children because most have severe anatomic and neurologic defects at the bladder outlet. We have had little success with medical stimulation of the bladder outlet to improve continence.

Other nonsurgical therapies include clean intermittent catheterization (CIC) to completely empty the bladder on a prearranged schedule. Intermittent catheterization remains the single most important contribution to the treatment of incontinence in children. In children with neuropathic bladder, intermittent catheterization alone will provide continence in 19%–24%.[11,12] The addition of anticholinergic medications, which lower bladder pressures and inhibit detrusor contractions, to CIC programs raised the continence rates to 68%–89%.[13,14] It is important to recognize that various authors have defined continence differently in the past. Whereas most patients gain some social or daytime continence with medical therapy, complete dryness is possible in less than one-third. Even if bladder outlet function is marginal, continence may be improved by maximizing other aspects, such as bladder storage capacity, with medication and emptying the bladder regularly with catheterization.

PROCEDURES TO INCREASE BLADDER OUTLET RESISTANCE

Once the bladder outlet has been identified as a cause of incontinence and medical therapy has been exhausted without acceptable improvement, the next options are surgical procedures to enhance bladder outlet resistance. This may be done by three basic surgical methods: procedures to change the suspension, support, or angle of the bladder outlet; procedures to compress the lumen of bladder outlet either with an external compression device or by injection of material under the mucosa; and procedures to reconfigure the bladder outlet into a more efficient continence valve.

Procedures to Suspend the Bladder Outlet

For the past century, inadequate support or insufficient elevation of the bladder neck and proximal urethra has been identified as a cause of urinary incontinence.[15] Inadequate suspension contributes to incontinence by making the bladder outlet too mobile, allowing it to descend into the pelvis. Normal suspension of the posterior bladder outlet is necessary to provide resistance from below to counter increased abdominal pressures from above, and thus compress the lumen. Suspension of the bladder outlet may be accomplished in several ways, including procedures that fasten the existing periurethral fascia to the anterior pelvic wall and procedures that reinforce the posterior bladder outlet with a sling made of fascia or some other external material.

In 1949, Marshall, Marchetti, and Krantz (MMK) introduced a procedure to improve stress incontinence by surgically elevating and suspending the bladder neck and proximal urethra.[16] The procedure is based on sewing the anterior vaginal fascia just lateral to the urethra and bladder neck to the cartilaginous portion of the symphysis pubis (Figure 56.2). These sutures suspend and support the bladder outlet and re-create its posterior angle. The MMK procedure was for many years the gold standard of incontinence surgery, and the concept is still critical in correcting these problems. Burch's procedure to suspend the bladder outlet from Cooper's ligament was another form of suspension that gained wide acceptance.[17]

Both suspension surgeries produce cure rates in patients with a pure stress incontinence of >90%.[18]

Today, suture suspension of the bladder outlet in children is utilized usually as an adjunct procedure with other incontinence surgery and helps to produce continence in up to 88% of patients.[19,20]

Pereya (1959), Stamey (1973), and Raz (1981) developed procedures that were also designed to elevate and suspend the weak bladder outlet.[21–23] They supported and elevated the bladder neck using sutures from the perivesical and periurethral fascia to the rectus abdominal fascia. These procedures were clear advances because they could be done through small incisions using long needles to place the suspension sutures (Figure 56.3). The surgeons could confirm correct suture placement at the time of the procedure with the cystoscope, and the patients suffered minimal discomfort.

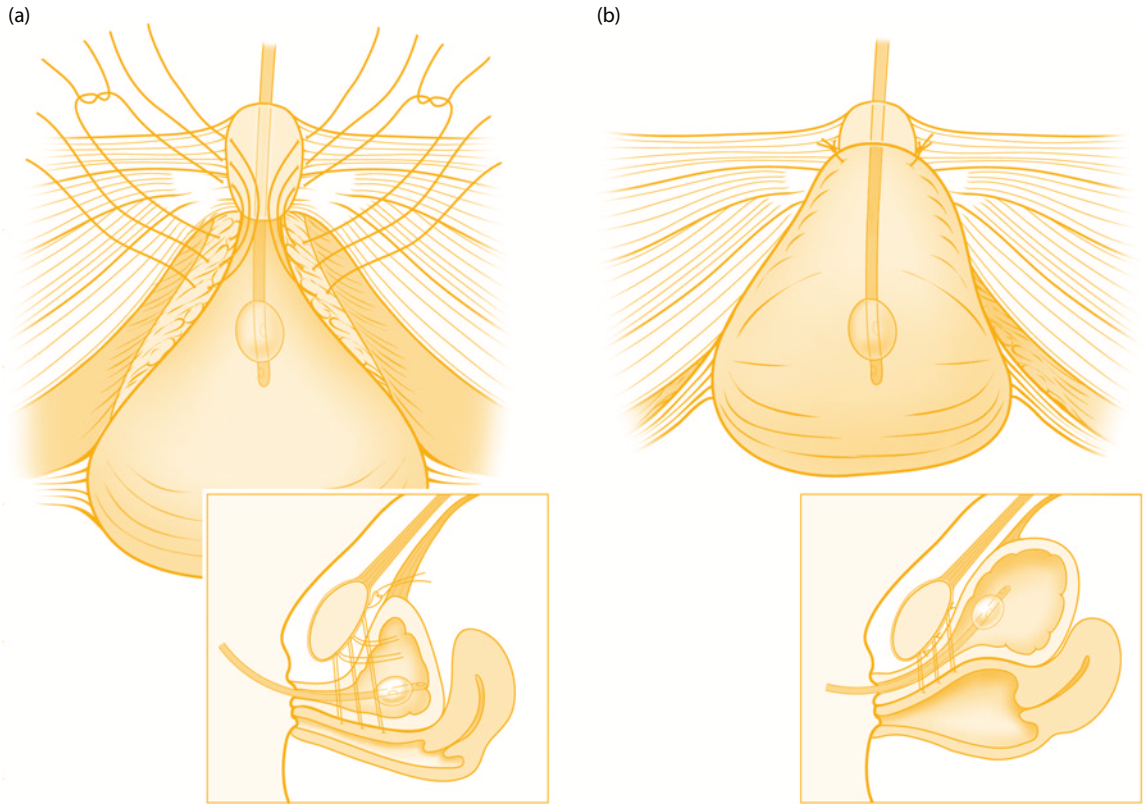

FIGURE 56.2 The Marshall–Marchetti–Krantz procedure elevates and suspends the bladder outlet, including the proximal urethra, by sewing the anterior vaginal fascia to the underside of the symphysis pubis. These are permanent sutures and re-create the posterior angle of the bladder neck. The concept of bladder neck suspension is still a cornerstone in incontinence surgery. (a) Placement of sutures between the anterior vaginal fascia and underside of the pubis. (b) Suspension and elevation of the bladder outlet.

McGuire improved on a concept introduced in 1911 by Goebell of suspending the bladder outlet with a sling of fascia or muscle.[24] McGuire developed a method of passing an isolated strip of rectus fascia beneath the bladder neck and reattaching it to the anterior abdominal wall at the insertion of the rectus fascia and the pubis (Figure 56.4).[25] Slings may improve continence by compressing the urethra, elevating the bladder outlet into the abdomen, or providing a stable point against which the urethra is compressed during increases in abdominal pressure.

This fascial sling and its variations have proven valuable for children with bladder outlet incompetence.[26]

The use of fascia under the bladder neck is more reliable in these children than sutures alone, which must rely on the strength of the native fascia adjacent to the bladder neck and proximal urethra to hold the suspension sutures.

At the time of open surgery, the most popular form of sling suspension involves a long strip of rectus fascia that is passed around the bladder outlet and sewn to the anterior abdominal wall fascia on each side. This suspension depends completely on the fascia to support the bladder outlet and is done entirely through a lower abdominal incision (Figure 56.5).

Slings may also be placed transvaginally in girls, just as is done in adults with good results.[27] This procedure would seem to be limited somewhat by the age of the child and size of the introitus. It is a useful approach in adolescent girls who are not undergoing simultaneous bladder reconstruction.

Bladder neck suspension, usually in the form of a rectus fascia sling, has been most helpful in girls with myelomeningocele on intermittent catheterization.[28] The female urethra is more easily manipulated in this way, and results have been good in this population, with continence rates of 78%–90%.[29–31]

The success rate in males in our hands has been considerably less than in females when suspension is used alone, although some authors report good experiences.[32–34,35] The combination of slings with other bladder neck surgery, such as narrowing the outlet, has been successful for some surgeons.[36]

Snodgrass reported an 82% continence rate in 17 patients who had a bladder neck repair and sling compared with a 45% success rate with slings alone.[37]

In the author's experience, the one group of patients who most often fail sling suspension is males who subject their bladder outlet to very high pressures that result from physical activity, such as ambulation and play.

Fascial sling suspension of the bladder outlet is not without complications. Decter has reported erosion of the sling into the bladder and late degeneration of detrusor compliance after sling placement.[38] Often, patients have difficulty catheterizing through the urethra after sling placement owing to the altered angle of the urethra. We

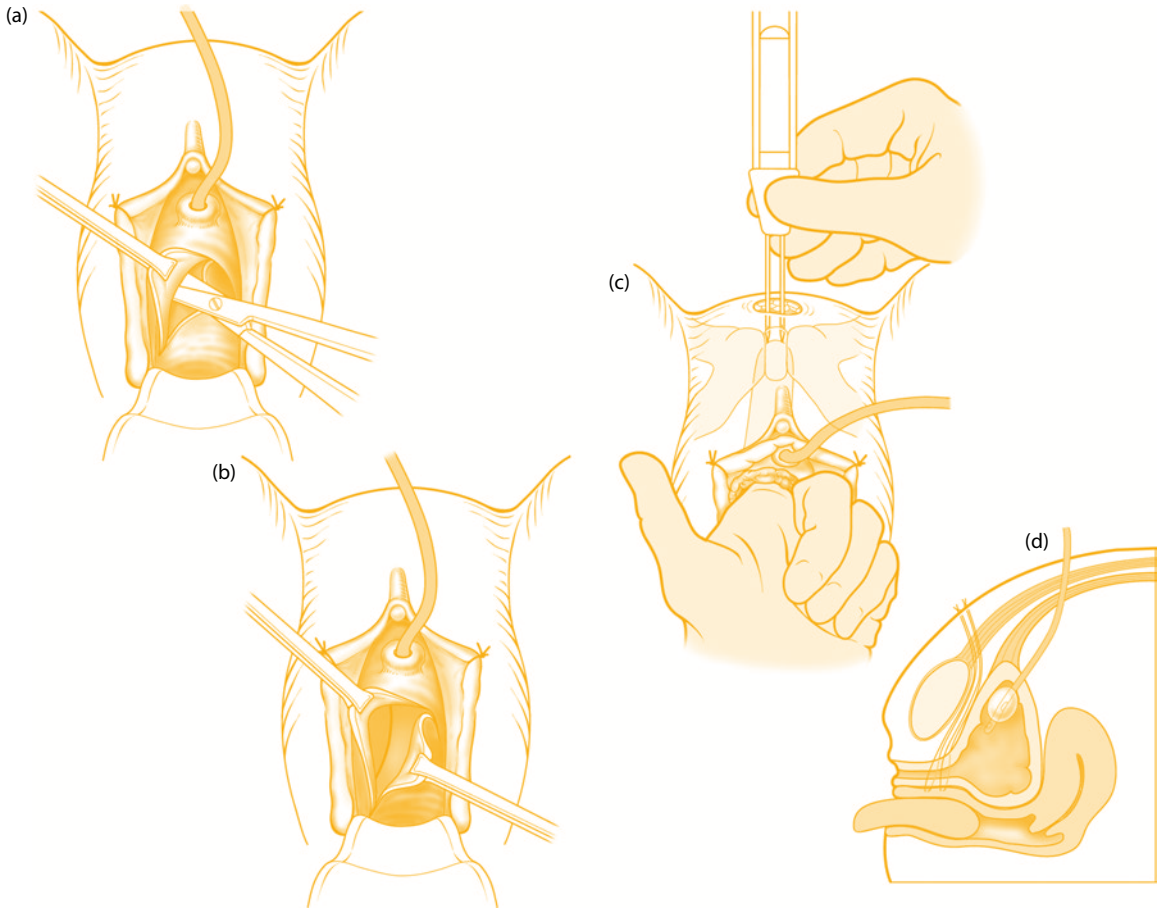

FIGURE 56.3 The Raz sling suspension uses long needles to pass permanent sutures from the anterior rectus fascia to suspend the bladder outlet from the anterior abdominal wall. The sutures support and elevate the bladder outlet and re-create the normal position and anatomy of the posterior bladder neck. They are dependent on the strength of the fascia surrounding the bladder neck and posterior urethra. (a and b) Exposure of the anterior vaginal fascia on either side of the bladder outlet. (c) Passing a needle from the anterior abdominal fascia to the vaginal incision in order to place sutures. (d) Suture suspension of the bladder outlet.

have also witnessed the sling break during physical activity, acutely returning the child to a state of incontinence. There has been concern about the effects of slings on erectile function in males with spina bifida, but this function appears to be preserved in more than 90% in one series of 14 patients.[39] Like many other procedures to improve bladder outlet resistance, augmentation cystoplasty has often been required to provide a large low-pressure reservoir for optimal continence.

Slings made of exogenous material have been introduced at various times and include true synthetic and processed biologic material, such as porcine small intestinal submucosa. The early-generation pure synthetics, such as silicone rubber and Gore-Tex, have a high risk of erosion into the urinary tract and are not in common use today.[40] A new generation of material is available, including synthetic polypropylene mesh tape. This material has been useful in adult stress incontinence and has a much lower risk of erosion than prior synthetic materials.[41,42] The use of newer synthetic mesh slings has yet to be documented in children, but their use in full-grown adolescents seems promising.

The processed porcine biomaterial, small intestinal submucosa, has been in use for some time and has similar efficacy for producing continence. It offers an off-the-shelf replacement for rectus fascia, thus shortening surgical time and simplifying abdominal wall closure at the time of reconstruction.[43,44]

Procedures to Compress the Weak Bladder Outlet

Surgery to compress the bladder neck externally can take one of two forms: variable or fixed. Since the normal bladder neck offers variable outlet resistance, this form is the most desirable, so that the resistance can be relaxed to allow voiding or easy catheterization. The artificial urinary sphincter developed by Scott et al. in 1972 has been valuable in the management of incontinence for many years.[45]

Artificial Urinary Sphincter

The artificial urinary sphincter is a hydraulic device that is composed of three parts: an inflatable cuff that surrounds and compresses the bladder neck or bulbous urethra, a pressure-generating balloon, and a pump control module (Figure 56.6). The artificial sphincter gives the patient the

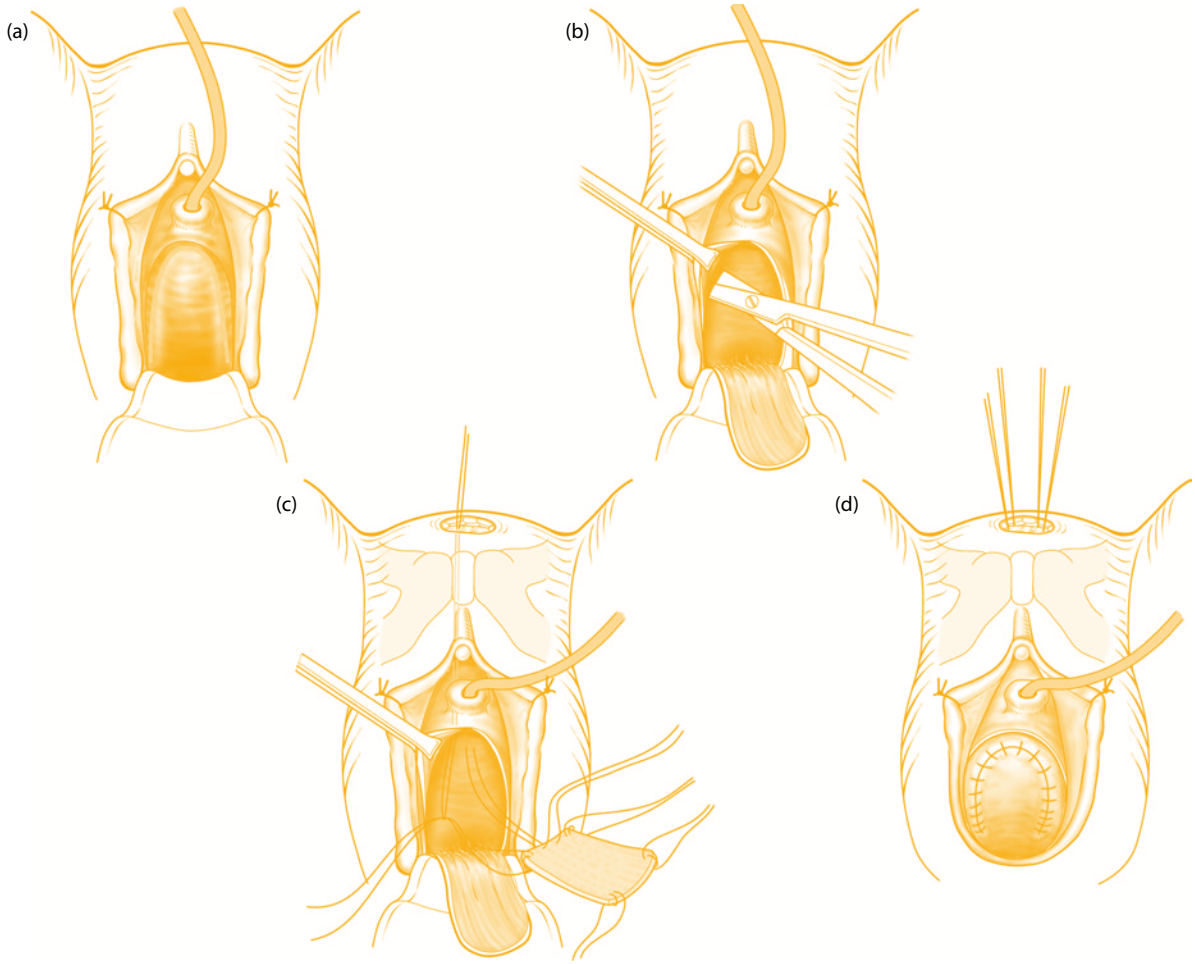

FIGURE 56.4 McGuire developed a suspension procedure that uses long sutures from the anterior abdominal wall to support a short strip of fascia. This fascia is passed posterior to the bladder outlet and supports and elevates the bladder outlet. This procedure provides more uniform support to the posterior bladder neck and does not rely on the native fascia around the bladder neck and urethra. (a) Vaginal incision to expose anterior vaginal fascia. (b) Dissection on either side of the bladder outlet. (c) Placement of the sling. (d) Sutures that elevate and suspend the bladder outlet.

ability to deflate the cuff and reduce the compression of the bladder neck at will. The pump is placed in the scrotum or labia, and the entire device is contained within the body. Continence rates are close to 90% after placement of the device.[46–48]

The bladder neck is the preferred site of placement in children (Figure 56.7). The usual minimal age for placement of artificial sphincters is 6 years for boys and 8 or 9 years for girls.[49] The pressure exerted on the urethra is regulated by the balloon or reservoir, and most children need 61–70 cmH_2O pressure to safely control the bladder outlet. The device is not activated immediately, as cuff pressure immediately after surgery may cause erosion of the cuff into the bladder. The sphincter may be activated after 6–8 weeks with less risk of erosion.[50]

Initially, there were concerns that performing intermittent catheterization through the implanted sphincter could cause damage to the tissue compressed by the cuff and lead to erosion. Sphincters were only placed in patients who could void, but as many as 50% of children cannot void efficiently after sphincter placement, making catheterization necessary.[51] Barrett and Furlow reported a series of children with neuropathic bladders who could not void after artificial sphincter surgery and found that intermittent catheterization could be performed safely if the cuff was deflated to pass the catheter.[52,53] Continence was good, and no patients suffered erosion due to catheterization. It appears that the ability to void may deteriorate with time, particularly in boys with neurogenic bladder. Gonzalez et al. reported that 74% of patients followed for a mean of 8 years after sphincter placement required intermittent catheterization.[47] Upsizing the sphincter cuff size in adolescent boys who suffer delayed voiding failure after sphincter placement has not been successful in restoring the ability to void.[54]

Historically, there has been a higher rate of reoperation with artificial sphincters than with bladder outlet reconfiguration.[55] This rate appears to be improving with better technique and newer devices. Kryger et al. reported an average of 0.03 revisions per year with the newest model, and 70% of children who had sphincters placed since 1987 have not required revision.[56] The long-term (7–10 years) survival of the artificial sphincter in children in two large series is approximately 80%, with most being lost

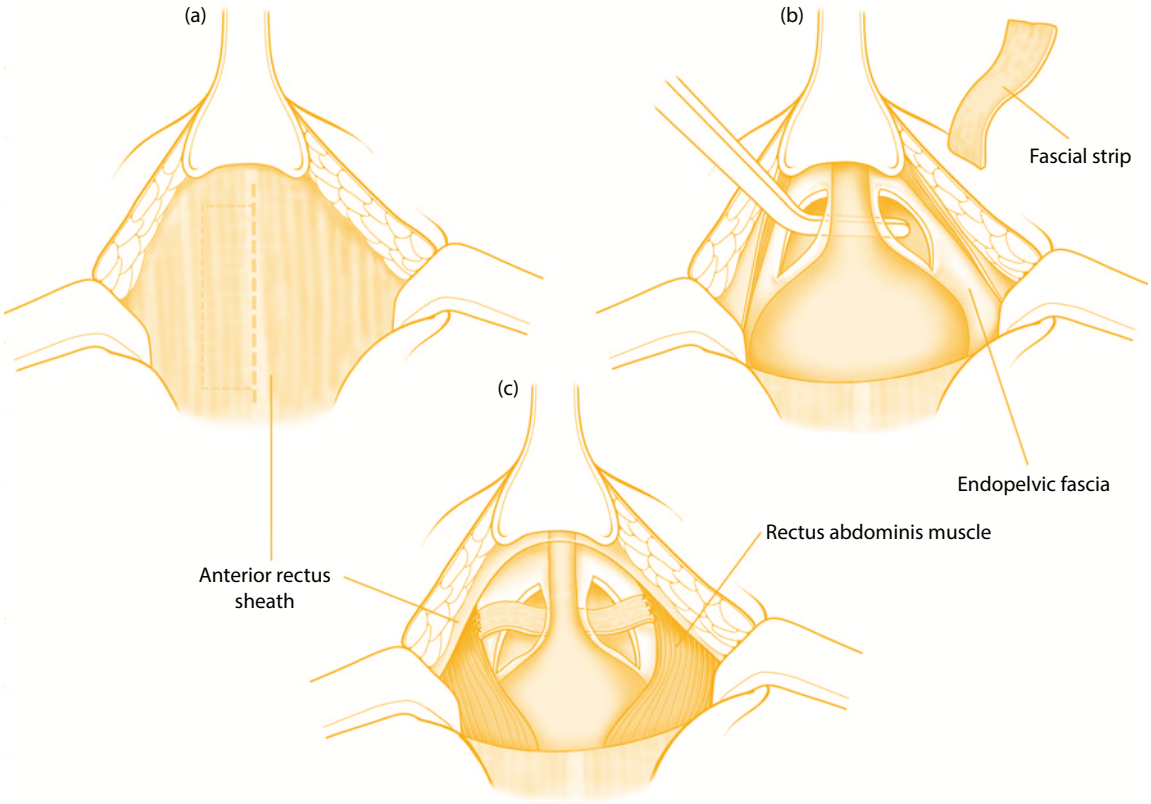

FIGURE 56.5 Fascial slings may be harvested from the anterior rectus fascia at the time of open surgery and used to suspend the bladder outlet from the anterior abdominal wall. (a) A single strip of fascia can be taken from the lateral aspect of a midline incision and (b) passed behind the bladder outlet. (c) Each end of the sling can then be sewn to the anterior rectus fascia on each side to elevate and support the bladder neck and urethra.

to the complications of device infection and erosion.[48,57] Eventually, all devices will wear out and fail, requiring replacement, but if complications can be avoided, the mean survival of the new devices in children is more than 12 years.[46] The newest model (AS 800), with a narrow backing cuff, was developed in 1988. It had a mechanical failure rate of 7.6%, a nonmechanical failure rate of 9%, and a sphincter survival rate of 92% in 184 adult patients, with a mean follow-up of 40.8 months.[58]

Roth and others reported an important complication of artificial sphincter placement in 1986 when they discovered that some patients suffered late deterioration of the upper urinary tracts.[59–61] This deterioration was due to two factors: a failure to void efficiently in some patients and the new development of detrusor hypertonicity in others. Deterioration of detrusor function after sphincter placement occurs in as many as 20% of patients, and there is currently no reliable method to predict which patients will undergo these changes or the timetable for risk.[57,62] Because of this threat, it is necessary to follow patients with artificial sphincters with upper tract imaging and urodynamics, as needed indefinitely after placement of the sphincter.

Augmentation cystoplasty, as either a simultaneous or later procedure with artificial sphincter placement, is necessary in approximately 30% of children.[47,63]

Augmentation increases storage volume and decreases storage pressures of the bladder due to poor compliance or hypercontractility of the detrusor. Augmentation may be performed at the same time as sphincter placement but has been associated with an increased risk of device infection if colon and small bowel are used for the augmentation.[64] Apparently, augmentation with the stomach does not present an increased risk of infection in simultaneous sphincter placement.[65]

Patient selection for artificial urinary sphincter is important. Although there has been an increased risk of erosion with girls who had prior bladder neck surgery, Bosco et al. have demonstrated that the risk to girls and boys is similar if they have not had prior bladder surgery.[66] The condition of the bladder outlet that will be compressed with the cuff is critical, and prior bladder neck surgery or excessive scarring increases the risk of erosion and infection.[67] Castera et al. have reported that prior bladder neck surgery also impacts the continence rate after sphincter placement, resulting in only 37.5% continence in this group.[68]

The artificial urinary sphincter is the only method of producing variable bladder outlet resistance and thereby allowing volitional voiding. Its main indication today is in children who have the ability to void prior to surgery and the potential to do so after placement of the device. Use of the artificial sphincter in patients who require augmentation and intermittent catheterization offers little advantage over other methods to increase bladder outlet resistance.

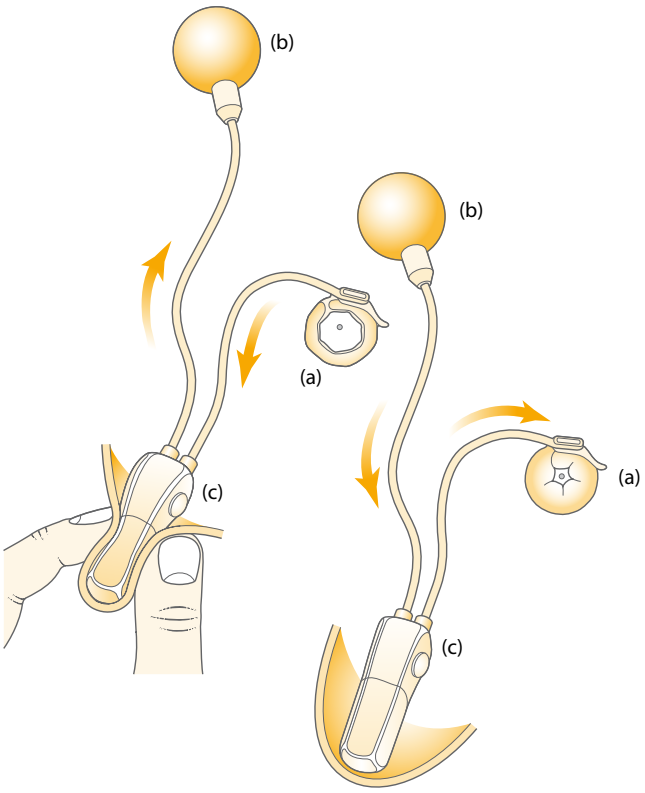

FIGURE 56.6 The artificial urinary sphincter is a mechanical device composed of three components: (a) an inflatable cuff, (b) a pressure-regulating reservoir balloon, and (c) a control pump. It functions by using hydraulic pressure to inflate the cuff, which compresses the urethra and provides continence. By squeezing the pump (implanted in the scrotum or labia), the patient can manually deflate the cuff and allow voiding or catheterization through the urethra. The pressure in the balloon then restores pressure throughout the system and reinflates the cuff in 3 minutes.

Bladder Outlet Wraps

There have been a few attempts to compress the bladder neck with a fixed resistance, and these have usually been in conjunction with bladder neck reconstruction surgery. Silicone rubber sheaths have been placed around the narrowed bladder neck, but in early series, more than 60% eroded into the lumen and required removal.[69] Quimby et al. presented a large series of 94 patients treated with silicone sheaths used in conjunction with a Young–Dees–Leadbetter (YDL) bladder neck reconstruction. The authors continued to modify their technique until the erosion rated dropped to 7% in 35 patients. This improvement was attributed to using omentum to wrap the sheath and using a single-layer short silicone wrap. Satisfactory continence in this group was achieved in 72% of patients with this method (Figure 56.8).[70] Two other groups have reported synthetic constrictors or cuffs. de O Vilar et al. reported a new device called a constrictor that compresses the bladder neck. It produced continence in all 42 patients in whom it was used; however, it had to be removed in 4 patients because of erosion or infection.[71] Kohn et al. presented a series of children treated with a purse-string cuff around the bladder neck made of polytetrafluoroethylene (PTFE) tubing surrounding woven polyester tape:[72] 75% of patients were dry after surgery, but 30% of the devices had to be removed because of complications.

Walker et al. described a procedure to wrap and compress the bladder neck circumferentially with rectus fascia with good results.[73] Some of their patients also needed bladder neck narrowing at the same time. Unlike silicone rubber, there were no erosions of the fascia, and postsurgery urodynamics showed that 70% of patients could not be made to leak at any pressure. Long-term follow-up of these patients indicates that the facial wrap and bladder dynamics are stable.[74] Bugg and Joseph presented a rectal fascia cinch that wraps around the bladder neck and is anchored to the pubis.[75] This procedure produced 60% continence. A myofascial flap made from rectus muscle can be used as a vascularized wrap and has been wrapped

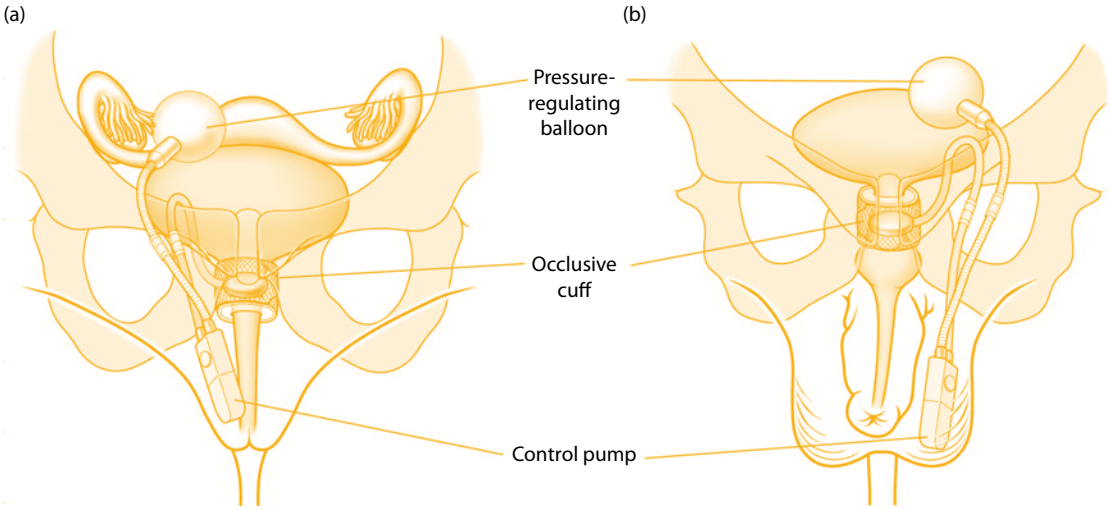

FIGURE 56.7 (a) Artificial urinary sphincter components in a female with the pump implanted in the labia. (b) Artificial urinary sphincter components in a male with the pump implanted in the scrotum. Both examples show the cuff implanted around the bladder neck.

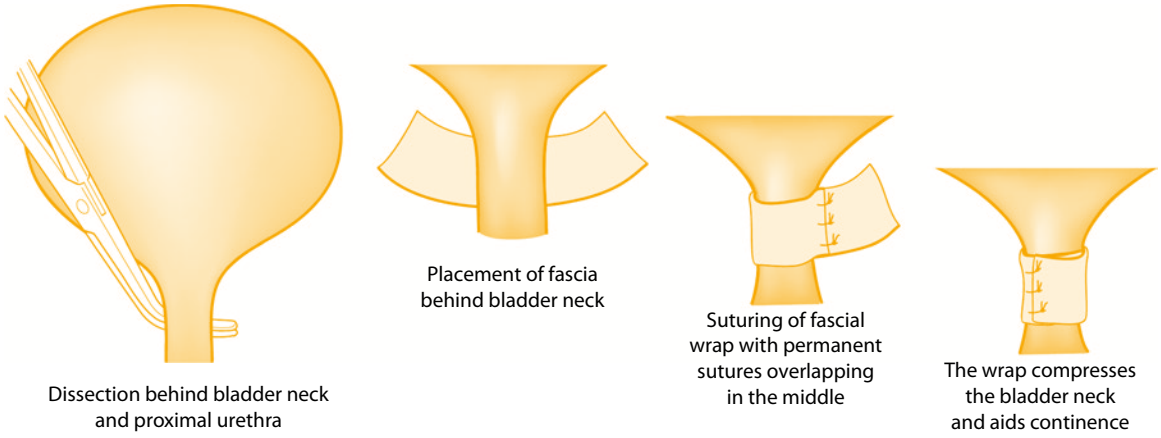

FIGURE 56.8 Walker described a fascial wrap of the bladder outlet in incontinent children. A strip of rectus fascia was harvested and wrapped around the bladder outlet and sewn together with permanent sutures. This provides consistent compression of the open bladder outlet and constant outlet resistance. Some patients with wide bladder outlets required bladder neck narrowing.

around the bladder neck and anchored to the pubic bone. This method has produced 75% continence in limited numbers.[76] Finally, a flap of bladder detrusor has been harvested and used to wrap around the bladder neck to compress the bladder neck.[77] Of course, any increase in fixed resistance at the bladder neck almost always precludes voiding and requires that the patient rely on CIC.

Injection Therapy of the Bladder Outlet

Several substances have been injected under the mucosa of the bladder neck in order to increase intraluminal pressure generated by the weak bladder outlet and provide continence. The first substance used in significant numbers of patients was PTFE paste or polytef.[78] Politano et al. popularized its use in adults and eventually applied the concept to children.[79,80]

They reported 86% success rates in patients who were incontinent from bladder neck surgery and 50% in patients with neuropathic bladder. Injection therapy was relatively easy to perform and required no incision, so it could be done on an outpatient basis. Unfortunately, particles of polytef were found to migrate to other organs in animal studies, and particles were found in pulmonary granulomas in a human after periurethral injection.[81,82] Safety concerns have caused abandonment of its use in the United States. A newer form of silicone, polydimethylsiloxane, or Macroplastique, has been used in Europe with continence achieved in 34% of patients.[83] It is not currently available in the United States. Other agents have been used, including autologous fat and collagen. Gonzalez de Garibay et al. reported periurethral injection of fat obtained from liposuction of the abdominal wall in 1989.[84] Initial success in treating incontinence was never as good as with polytef, and the effects diminished with time because the fat did not survive due to poor neovascularity.[85] Eventually, 80%–90% of the injected fat was absorbed by the local tissue.

Gluteraldehyde cross-linked collagen has been one of the most common agents used to increase bladder outlet resistance. It has been used in the same manner as polytef paste and is injected beneath the mucosa using a needle passed through a cystoscope (Figure 56.9). The success in treating children with incontinence has been inconsistent, with around 50%–88% of patients considered to have a good result and 20%–63% becoming dry.[86,87] Bomalaski et al. reported a large series of collagen injections in children in 1996.[88]

They reported a 22% cure rate of incontinence in 40 children, with improvement in another 54%. Of those patients with a mean follow-up of 4.5 years, the cure or improvement rate remained stable over time. Other clinicians have noted the biologic degradation of collagen and expressed concern about long-term durability.[89] Kassouf et al. demonstrated poor results with collagen injections, in children with neuropathic bladder dysfunction. Only 20% of their patients improved after injection, and all these eventually deteriorated within 2 months of treatment.[90]

The limited success and potential degradation should be explained to the patient and family. Also, 2.5% of patients are allergic to the collagen from dietary exposure, and an additional 0.9% may develop late hypersensitivity.[91] Preoperative skin testing is necessary to establish that the patient does not have antibodies to the collagen and is less likely to react to the injection.

The newest agent to be used for injection of the bladder neck for incontinence is Deflux (dextranomer/hyaluronic acid copolymer). We have injected Deflux into the bladder neck of 16 children with bladder outlet incompetence. Of the 12 with neuropathic bladder, 25% were dry and an additional 33% improved after injection therapy, with a mean follow-up of only 9 months. None of the patients with other causes of incontinence achieved continence, whereas 33% showed improvement. No patients who performed intermittent catheterization through their urethra improved.[92] Dyer et al. reported on 34 patients who were treated primarily with injection therapy using either Deflux or Teflon Paste. Only four children had improved continence with injection alone.[93] Alova et al. presented a 39% failure rate in 89 patients who had primary Deflux injection therapy, noting that repeat injections have a very low success rate. They note that the presence of Deflux in the bladder neck does not impede secondary surgical bladder neck repair.[94] Lottmann et al. reported a gradual degradation of continence in patients treated primarily with

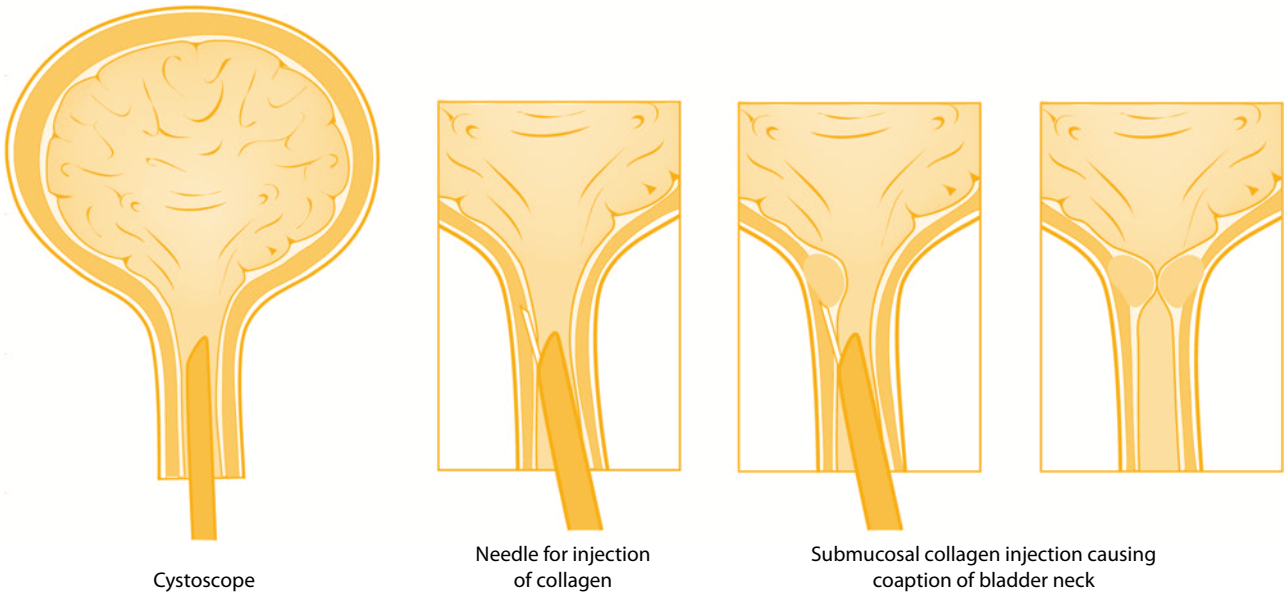

FIGURE 56.9 Injection of the bladder neck with various materials, such as polytef paste and collagen solutions, has been used with more success in adults than in children. The needle is passed through a cystoscope and the material is injected submucosally either from the urethra or from a suprapubic approach. The material provides passive pressure to help to occlude the bladder outlet.

Deflux from an initial dry rate of 79% at 1 month to 40% at 7 years, with a rapid drop in the first year to 52%.[95]

With the widespread use of catheterizable urinary stomas in children with neuropathic incontinence, antegrade bladder neck injection of bulking agents through the catheterization channel has merit. The visualization of the bladder outlet from above is superior to the visualization from the urethra.

These mixed findings have limited injection therapy in most pediatric urologist's hands to incontinent patients who have had failed bladder neck reconstruction surgery. Up to 50% of these patients may become dry with injection therapy, but some require multiple injections.[96] This is a simple and safe outpatient procedure, but the results may degrade with time and its effects may diminish.

Surgical Reconfiguration of the Bladder Outlet

Young–Dees–Leadbetter Procedure

In 1922, Hugh Young presented a refined procedure to reconfigure the inadequate bladder outlet in epispadiac patients who were incontinent due to bladder outlet incontinence.[97] Young had altered his approach from narrowing the posterior bladder outlet to narrowing the anterior urethral and bladder neck. He excised a full-thickness strip of tissue from the "funnel-like neck" of the bladder and reapproximated the sides with a single row of chromic catgut sutures to create a more normal appearance (Figure 56.10). Ureterosigmoidostomy diversion was the accepted surgical treatment of incontinence due to epispadias and exstrophy prior to Young's procedure.[98] Young was obviously pleased with the results of his procedure and reported, "No fistula, no stricture, perfect urinary control, sexual powers normal." For more than 25 years after Young first presented his method to reconfigure the bladder neck for epispadias, his procedure remained the best surgical treatment for urinary incontinence due to a weak bladder outlet.

In 1949, John Dees improved upon Young's procedure by extending the posterior urethral flap into the bladder and removing the mucosa from the muscle on the lateral aspect of this flap. This posterior strip of urethra and bladder was then closed in two layers, mucosa and muscle, to form a neourethra (Figure 56.11).[99] Whereas Young had been content to narrow the proximal urethra and bladder neck, Dees changed the position of the bladder neck itself. He created a long neourethra from tissue that normally would have been the posterior bladder wall. The result was to move the bladder outlet higher into the pelvis and provide a longer, more muscular, urethra.

In 1964, Guy Leadbetter advanced this concept further by extending the posterior bladder flap even higher into the bladder.[100] This was made possible by moving the ureters from their normal location to a more cranial position further from the urethra and original bladder neck. The position of the ureters had been the limiting factor when Dees created his neourethra and moved the bladder neck above its natural location. Leadbetter moved the ureters out of the way by mobilizing them and reimplanting them transversely across the posterior bladder wall well above the trigone.

By extending the neourethra higher in the bladder, Leadbetter was also presented with a wider strip of bladder to use for his neourethra. A narrow strip of mucosa was left in the central portion of the neourethra. This was tubularized, the entire mucosa lateral to the strip was excised, and the two flaps of muscle lateral to the neourethra were then wrapped over the mucosa in an overlapping fashion, providing additional muscular support to the neourethra and bladder neck (Figure 56.12). With few changes today, the YDL bladder neck repair remains the gold standard of bladder neck reconstruction. Continence has been obtained in 78% of patients with neuropathic bladders and in 80% of exstrophy patients.[101–103] It must

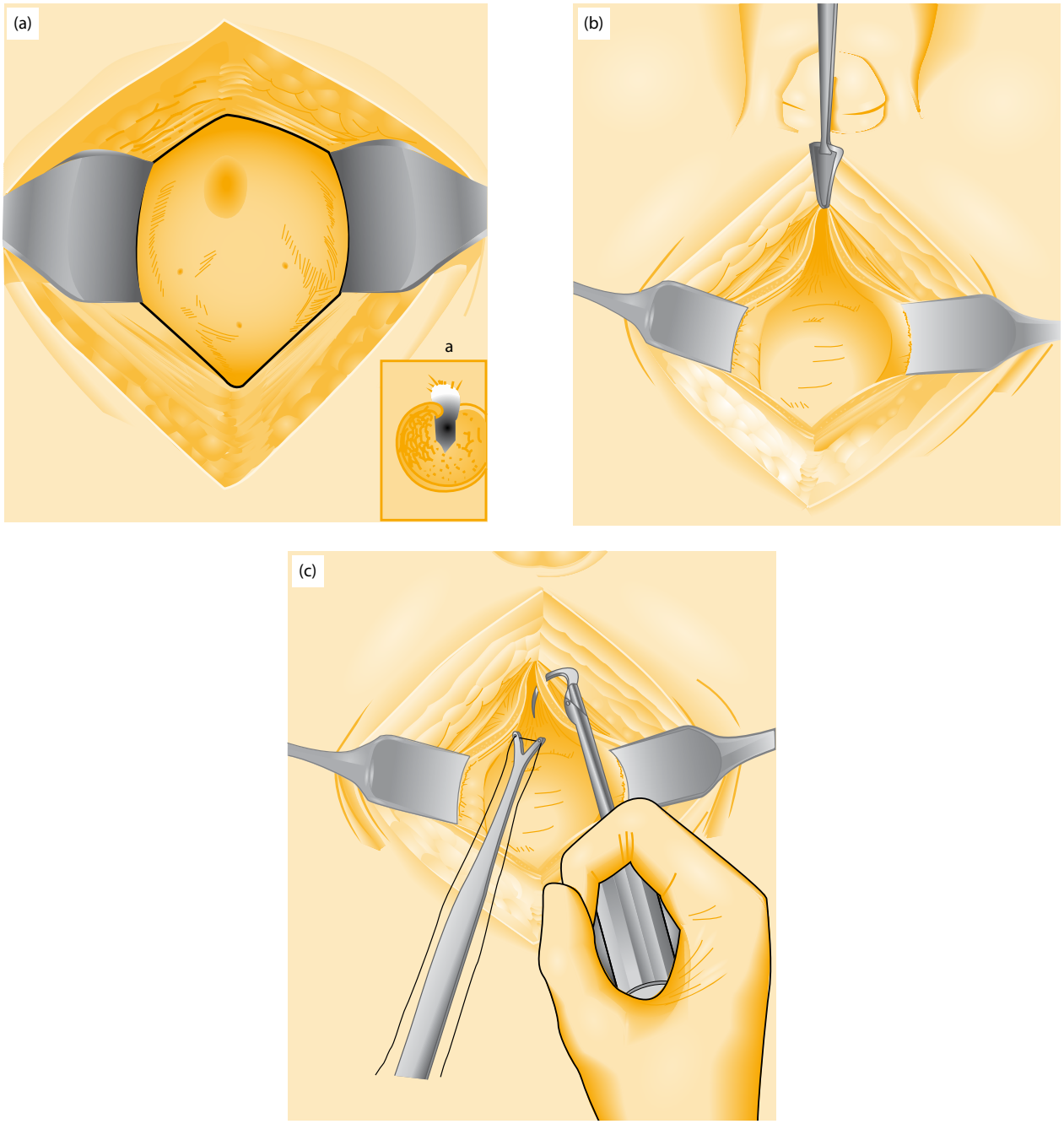

FIGURE 56.10 Young's original bladder neck repair was essentially an excision and narrowing of the outlet. He excised a full-thickness strip of mucosa and muscle from the bladder neck and proximal urethra and closed it with a single row of sutures to create a more normal-appearing bladder neck when viewed from within the bladder. This, in essence, lengthened the urethra and placed the bladder neck higher in the pelvis. (a) Open bladder outlet viewed from above. The inset shows Young's view of epispadias with incontinence. (b) Excision of the strip of mucosa and muscle. (c) Narrowing of the bladder outlet using Young's instrument to pass suture.

be noted that augmentation cystoplasty was necessary to obtain this degree of continence in 90% of the neuropathic bladder children in our series and in 50% of the exstrophy–epispadias patients in the Mayo Clinic series.

Disadvantages of the YDL bladder neck reconstruction include loss of significant bladder capacity that results from the reallocation of bladder wall tissue to the urethral continence mechanism. The neourethra may be tortuous and difficult to catheterize.

Variations of the Young–Dees–Leadbetter Procedure

Of the many variations to the YDL, that of Mollard is closest to the original.[104] He creates a 7 cm long urethral strip that is wide enough to close over a 10 Fr catheter and removes the mucosa from the triangular muscle flaps lateral to the strip. He then incises one of the periurethral muscular flaps vertically parallel to the strip and rotates it horizontally across the midline in order to develop an

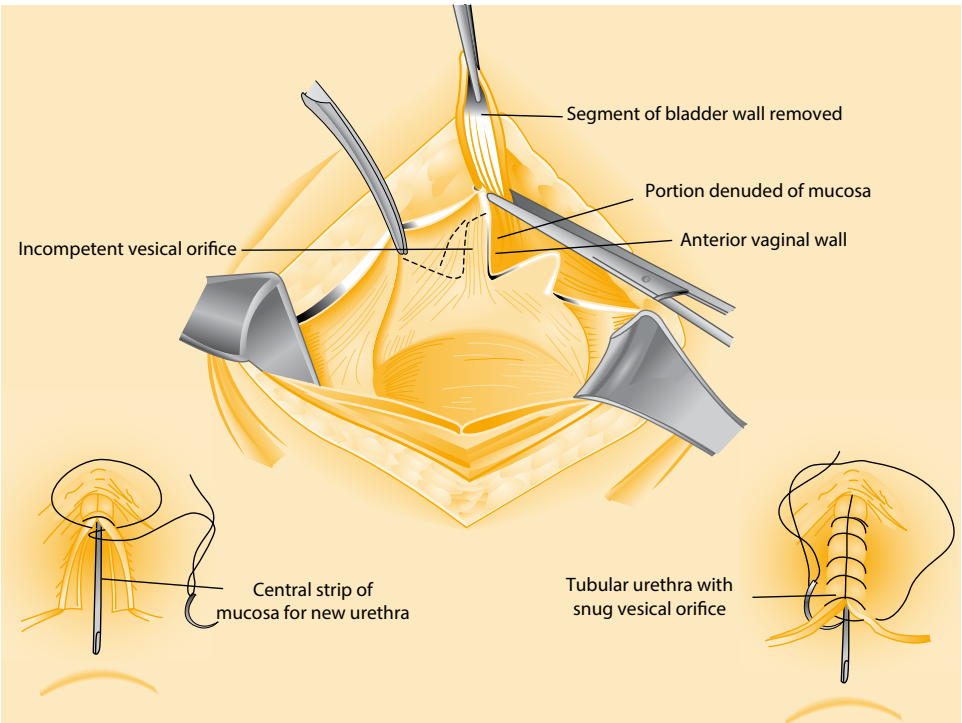

FIGURE 56.11 Dee's revision of Young's procedure extended the posterior urethral flap into the bladder and allowed a longer neourethra. He removed the mucosa from the muscle on the lateral aspect of this flap, and after closing the central flap of mucosa into a tube, he closed the muscle over the mucosa in a second layer. This provided additional muscle around the neourethra.

anterior bladder neck angle (Figure 56.13). Mollard's procedure has been applied mostly in exstrophy patients, and he has achieved a 70% continence rate.

Koff's variation on the YDL also differs from the original in its use of the periurethral muscle flaps.[105]

Koff's initial incision is on the lateral aspect of the bladder neck, rather than the midline, and this produces a single long muscle flap on one side of the bladder. After he moves the ureters cephalad, Koff then strips the mucosa from the long muscle flap, leaving a midline strip of urethra and bladder to tubularize for the neourethra. The long muscle flap is then wrapped around the neourethra, producing what he has termed "the cinch" (Figure 56.14). Koff has achieved 80% continence rates in mostly exstrophy patients. All the patients have had significant difficulties voiding. Forty percent of the children required bladder augmentation and intermittent catheterization. Bladder capacity is lost to a similar degree as in the YDL procedure.

Mitchell returned to Young's original concept of a narrowed neourethra without added muscular support.[106] He noted that overlapping bladder muscle flaps used to create more outlet resistance made the bladder smaller by reducing the bladder itself. Mitchell's procedure is the only bladder neck repair that does not decrease bladder capacity, as the anterior bladder and urethral flap are incorporated into the bladder (Figure 56.15). He mobilized a triangular full-thickness flap of anterior urethra and bladder neck and then narrowed the bladder outlet. The flap was then rotated cephalad and integrated into the bladder. Continence was achieved in 64% of patients, who all voided and were a mixed group of children including neuropathic bladders and exstrophy.

Some other variations of the YDL procedure have been developed, including Koyle's Thiersch–Duplay type tubularization of the posterior bladder wall.[107]

This procedure isolates and rolls a strip of mucosa into a tube in situ and then closes muscle and mucosa over the tube by rolling in the lateral tissue (Figure 56.16). He calls this the reverse Kropp or Ppork repair, and has achieved 82% continence in neuropathic bladder patients. There may be problems with catheterization per urethra, and therefore all of his patients had an alternative access for bladder catheterization. Chrizan et al. reported on a variation of Koyle's procedure that is done using the laparoscope within the bladder and basically forms a mucosal tube of the anterior bladder wall. It was performed on eight patients who had failed previous surgery. Six of eight were improved and four were dry. Operative time and hospital stay were less than with open procedures.[108]

Arap et al. presented the most radical variation of the YDL posterior-tube bladder neck repair for use in the most severe cases of exstrophy with tiny bladder plates.[109]

Their procedure is performed in two stages: the first stage is creation of a colon conduit with antirefluxing ureterocolonic anastomosis; the second procedure creates a tube in the same manner as the YDL procedure, but uses the entire bladder except for the dome, which is left open as a wide funnel (Figure 56.17).

The previously created colon conduit is then reconfigured as a reservoir and attached to the funneled bladder plate. Arap reported a 75% continence rate with patients voiding frequently. Intermittent catheterization has provided continence and allowed a long dry interval in our limited experience with the Arap procedure.

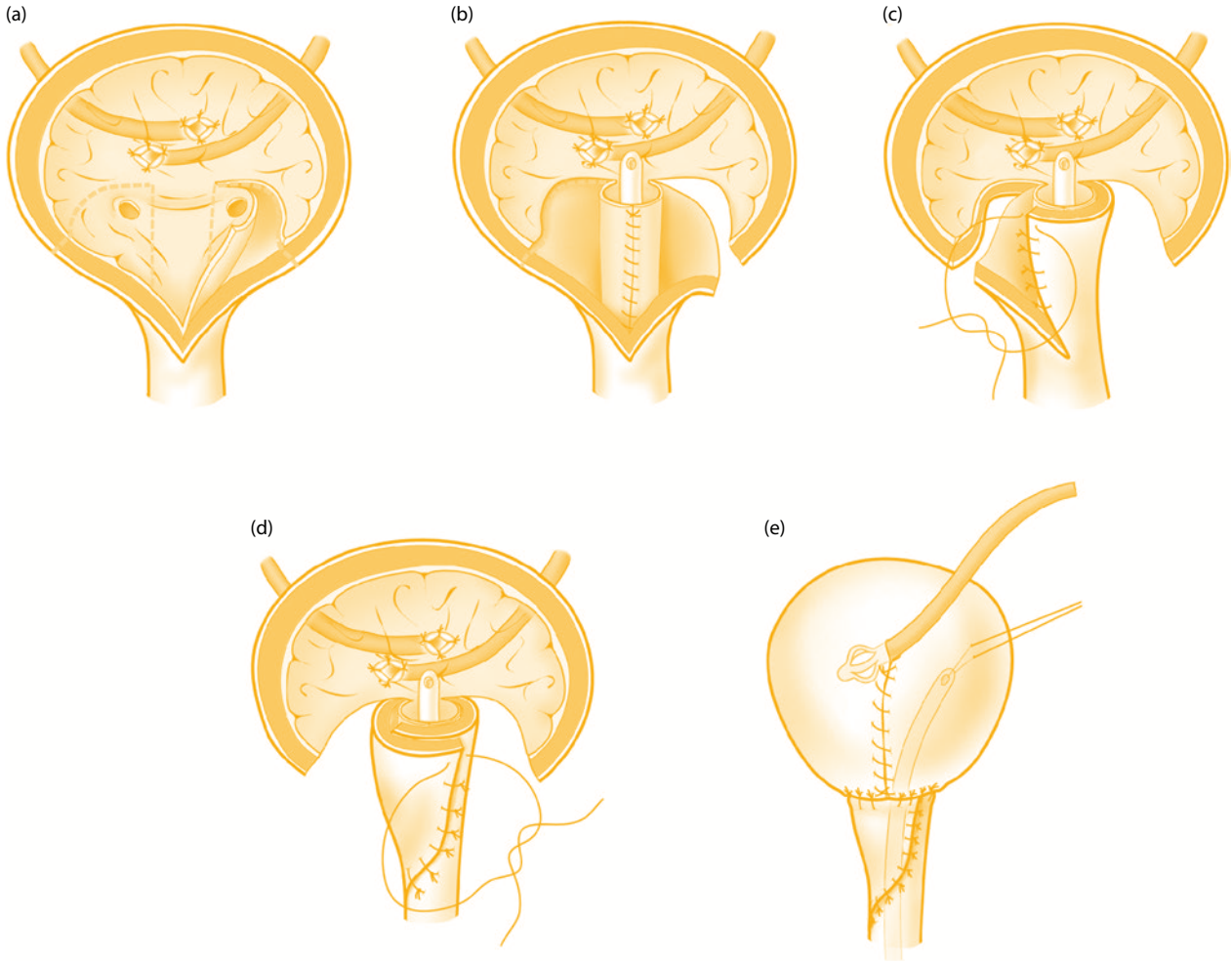

FIGURE 56.12 Leadbetter further improved on the Young–Dees bladder neck repair by moving the ureters to a new location higher along the posterior bladder wall and away from the urethra. This maneuver allowed the posterior bladder strip to be even longer and produce a long neourethra and a much higher bladder neck. (a and b) Leadbetter removed the mucosa from the triangular flaps of bladder muscle on each side of the mucosal strip that was to be used for the neourethra. (c) After rolling the strip into a tube for the neourethra, he closed the lateral muscle flaps over the neourethra in layers to provide even more muscle at the bladder outlet. (d) Muscle is rotated over the neourethra in an overlapping fashion. (e) Dependable bladder drainage is necessary.

Tanagho Bladder Neck Repair

In 1968, Tanagho was studying function and anatomy of bladder muscle when he noticed "a condensation of circle fibers above the internal meatus."[110] He then designed the first anterior bladder tube repair for incontinence and perfected it in dogs.[111] Three years later, he presented his experience in patients, including postprostatectomy adults.[112]

Tanagho intended to capture the muscle fibers of the anterior bladder and incorporate them into the bladder neck. He created a bladder-based flap from the anterior bladder just proximal to the urethra and rolled it into a tube for the neourethra (Figure 56.18). He then divided the urethra from the original bladder neck and anastomosed the neourethra to the native urethra end to end. The effect of this maneuver was to lengthen the urethra and create a new, more cephalad bladder neck.

Tanagho achieved a 72% continence rate and patients voided well. He compared his long-term results in 50 patients with the YDL procedure performed in 25 patients and found a 70% success with the Tanagho anterior bladder tube compared with 52% with the YDL posterior tube.[113] One advantage of Tanagho's bladder-based anterior flap was its applicability to short urethras, as demonstrated by Diamond and Ransley in urogenital sinus patients.[114]

This application remains as the most likely used of the Tanagho repair in children today. Disadvantages include the necessity to divide the bladder from the urethra, possibly resulting in difficult catheterization, and loss of bladder volume.

Kropp Bladder Neck Repair

In 1972, Jack Lapides made a contribution that forever changed our attitude and approach toward incontinence surgery.[115] His introduction of CIC controlled infection decreased bladder pressure and made many patients continent without further surgery.[116] CIC made voiding an option rather than a requirement, and changed the goals and results of incontinence surgery.

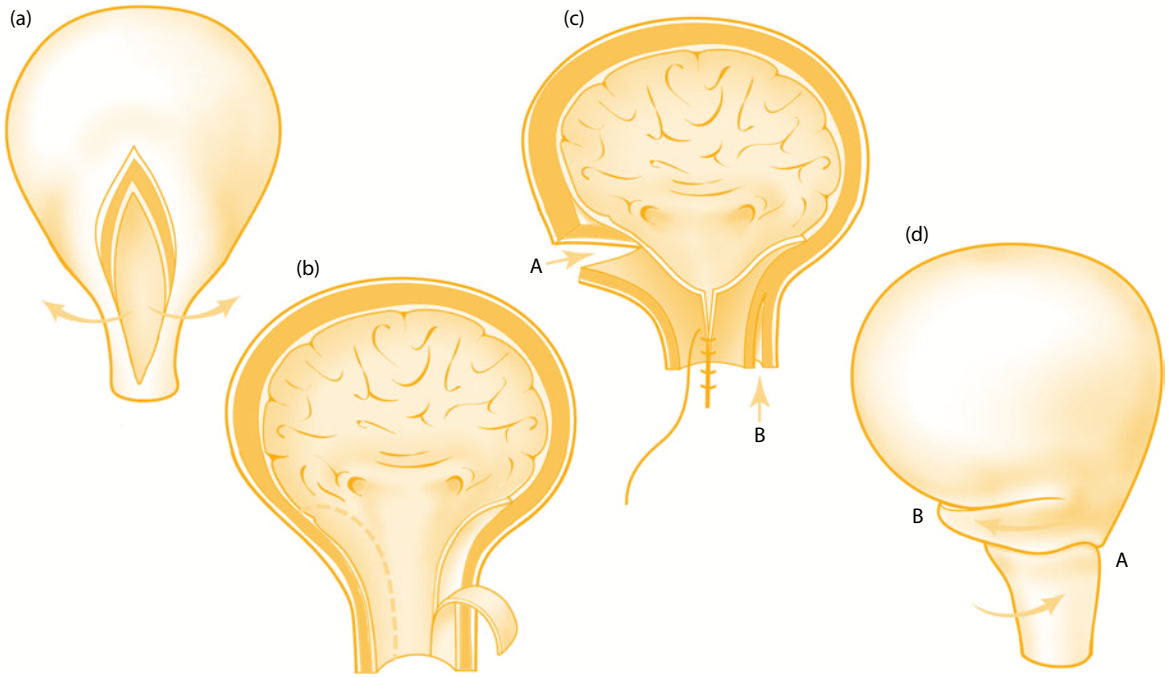

FIGURE 56.13 Mollard's variation of the YDL procedure is similar in its construction of the neourethra from a long posterior strip of urethra and bladder. It differs in that one of the two triangular flaps is incised vertically and parallel to the neourethra. This flap is then rotated horizontally across the midline to create an angle of the anterior bladder neck. (a) The bladder is opened in the midline. (b) The mucosa lateral to the central urethal strip is excised. (c) The two lateral muscle flaps are incised, one vertically and one horizontally. (d) Flap A is wrapped around the neourethra like the YDL operation, while flap B is rotated horizontally across the repair to create an anterior bladder neck.

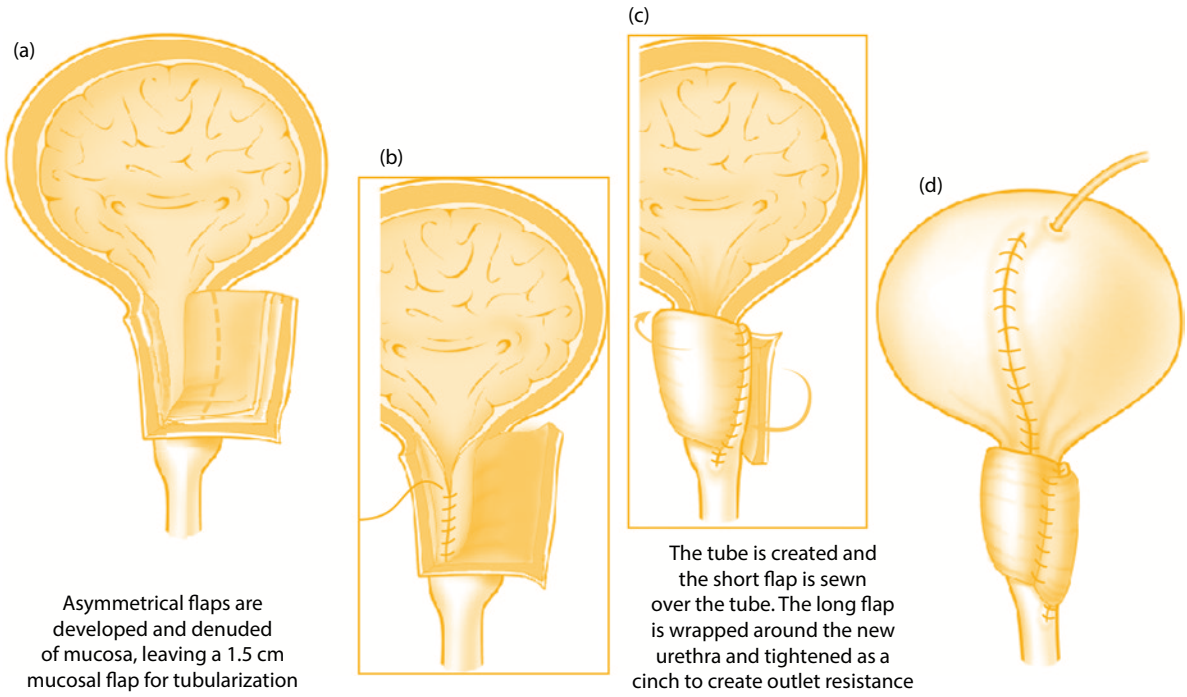

FIGURE 56.14 Koff's variation of the YDL procedure also creates the neourethra from a posterior flap of urethra and bladder and covers it with a flap of demucosalized muscle. The construction of this flap is different from other repairs that rely on two flaps. Koff makes a lateral incision of the bladder neck instead of opening the midline. This creates a single long flap on one side of the neourethra. The flap is then wrapped around the neourethra and sewn to itself with permanent sutures. It acts as a constant compression of the bladder outlet. (a) The bladder outlet is opened on one side. (b) A midline mucosal strip is tubularized, and the mucosa is dissected from the remaining muscle flap. (c and d) The muscle flap is then rotated around the bladder outlet.

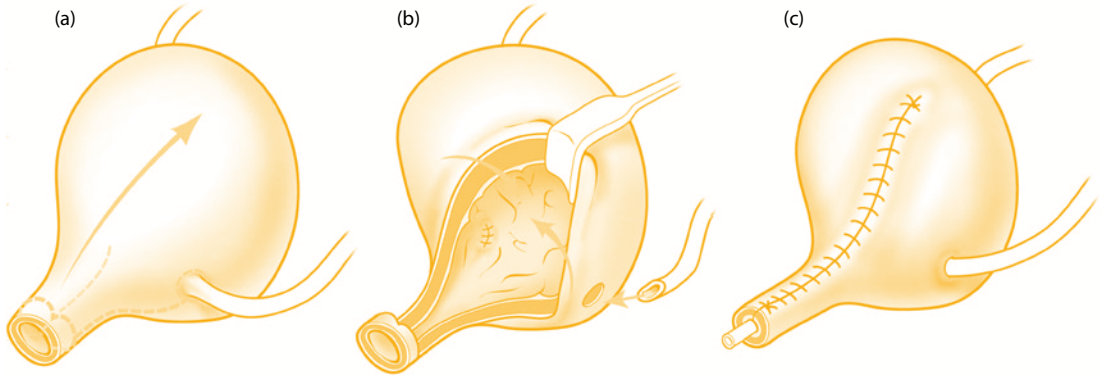

FIGURE 56.15 Mitchell returned to Young's original concept of a narrowed bladder neck that is not reinforced with additional muscle layers. His repair mobilizes a triangular flap of anterior bladder and urethra based on the bladder-side blood supply and then rotates the flap into the bladder. It is the only repair that does not decrease bladder volume. (a) An incision is made across the anterior urethra, extending up along the posterior lateral wall of the bladder outlet on each side. (b) The flap of bladder and urethra is rotated back into the bladder. (c) The incision is closed in the midline.

Kropp was the first surgeon to develop a new bladder neck reconstruction designed to take full advantage of CIC.[117] The goals of the surgery had changed. Dryness was foremost, and voiding was no longer a consideration. CIC had been used in patients with other forms of bladder neck reconstruction before this, but they were all procedures that allowed the patient to void, at least in theory. The Kropp procedure was the first to preclude voiding.

The Kropp procedure uses a full-thickness flap of anterior bladder muscle. This flap is based on the urethra, unlike Tanagho's flap, which is based on the bladder. The full-thickness bladder flap is isolated from the bladder and rolled into a tube of the same diameter as the urethra. The tube is then reimplanted in a submucosal tunnel in the midline of the posterior bladder wall between the ureters (Figure 56.19).

Advantages of Kropp's reconstruction included a very high continence rate of 80%–94%.[118,119] Kropp's strict definition of continence has been complete dryness or rare leakage. The reoperation rate was high in the original series, but most secondary procedures involved the storage function of the bladder, and only 20% of patients required additional surgery to the bladder outlet. To facilitate storage and to compensate for bladder volume lost in construction of the tube, Kropp now suggests that all patients undergo a simultaneous bladder augmentation. There have been problems catheterizing through the repair, but the improvement of leaving lateral attachments at the bladder neck intact and not completely separating the neourethra from the bladder has minimized this difficulty.

In 1997, Snodgrass reported a series of 22 children treated with the modified Kropp procedure described by Belman and Kaplan.[119,120] Snodgrass created a urethral-based flap of anterior bladder wall and rolled it into a tube. He did not divide the bladder neck from the remainder of the bladder. The posterior bladder mucosa is then incised in the midline to create a trough, and the tube is laid in this trough with the mucosa closed over the tube

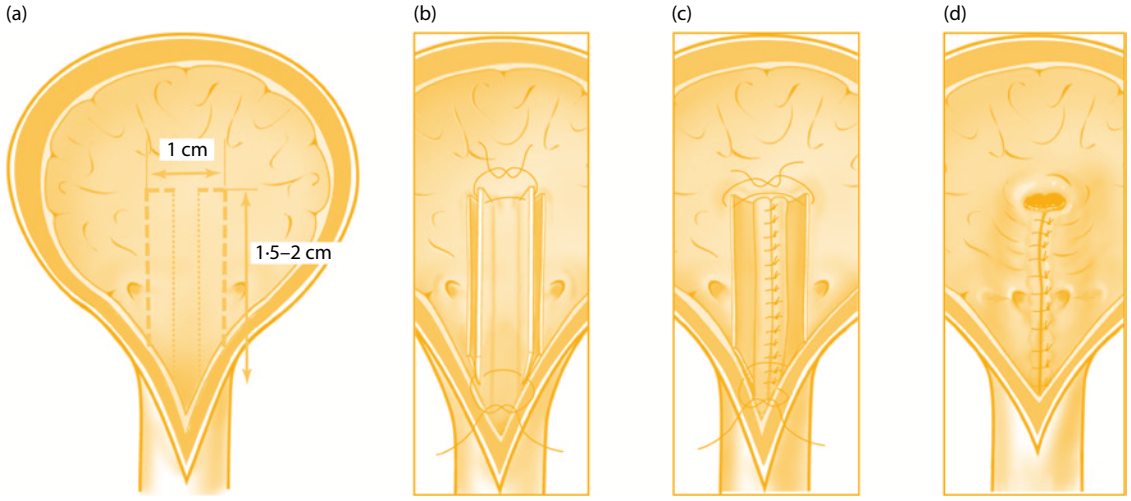

FIGURE 56.16 Koyle presented a bladder neck reconfiguration that isolates a strip of posterior mucosa in the posterior midline of the bladder. This strip is then rolled into a tube, creating a neourethra. Finally, the neourethra is covered with flaps of muscle and mucosa that have been mobilized lateral to the neourethra. (a) A mucosal flap is outlined. (b) The flap is then tubularized. (c) A second layer of muscle is closed. (d) Lateral mucosa is closed over the tube.

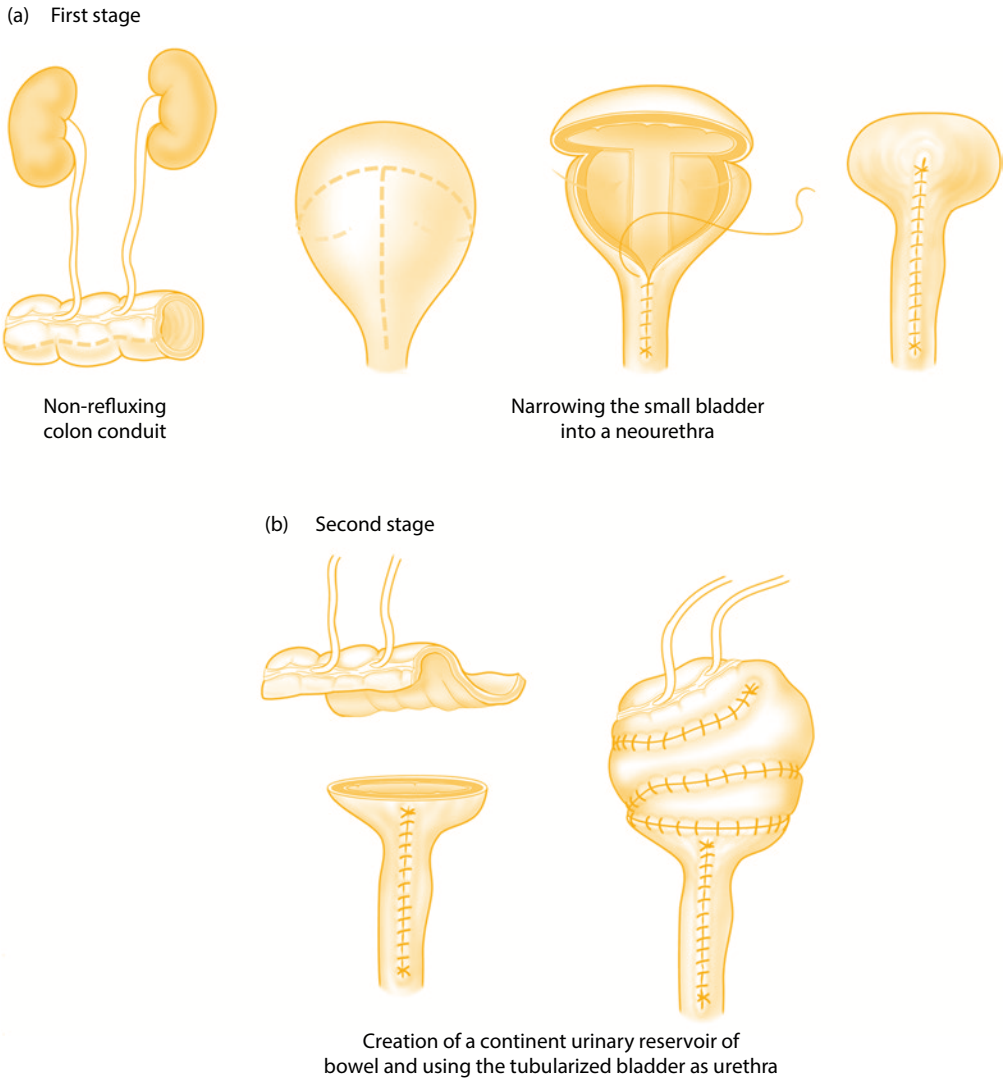

FIGURE 56.17 Arap's staged bladder reconstruction is the most radical reconfiguration of the bladder outlet. In the first stage, the ureters are transplanted from the bladder plate to a nonrefluxing anastomosis into a colon conduit. The second procedure creates a neourethra from the entire bladder except for the dome, which is left open as a wide funnel. The colon conduit is then reconfigured as a reservoir and sewn to the funneled bladder.

(Figure 56.20). No attempt is made to tunnel the tube. He reported a 91% continence rate, defined as dry intervals of 3 hours. Snodgrass notes that these patients are socially continent and will have slight leakage when catheterization is delayed. Bladder augmentation was performed in 91% of his patients at the same time as bladder outlet surgery. Just as in the original Kropp procedure, voiding is impossible.

Pippi Salle Bladder Neck Repair

Pippi Salle developed a bladder outlet repair for incontinence by creating a neourethra composed of both anterior and posterior bladder flaps.[121] This flap valve continence mechanism produces the only neourethra made of two separate flaps. Both anterior and posterior strips of bladder are isolated, and the anterior flap is completely mobilized as a flap based on the urethra. The posterior flap is outlined with two parallel mucosal incisions, and the posterior bladder muscle is left intact. The anterior bladder flap is then flipped down to oppose the posterior flap at the level of the posterior bladder wall. The two flaps are sewn together, creating a neourethra, which extends above the level of the ureters (Figure 56.21). Mucosa on either side of the strip of posterior bladder wall is mobilized, and the muscle from the anterior strip is sewn to the muscle of the posterior bladder. The complete-thickness bladder tube is then covered with the previously mobilized bladder mucosa just lateral to the tube.

The Pippi Salle repair produces continence rates of 80%, and this repair is easy to catheterize primarily because the posterior wall remains intact.[122] Bladder volume is decreased by the use of bladder wall to create the continence mechanism. This repair also requires the patient to catheterize, as voiding is impossible. McLorie and Khoury have warned about the potential danger of damaging the blood supply while isolating the long, thin anterior bladder flap.[123]

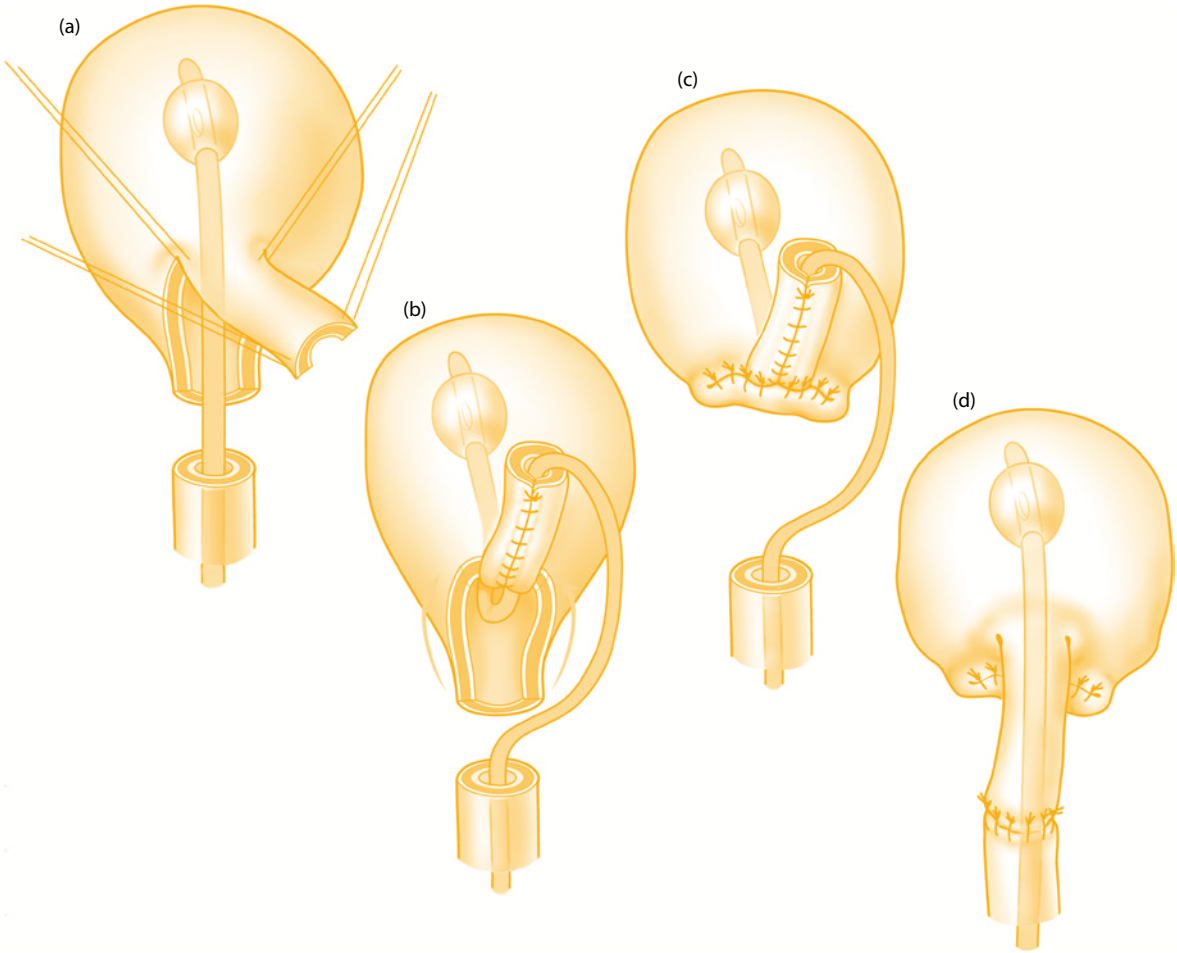

FIGURE 56.18 Tanagho's procedure created a neourethra from a strip of the anterior bladder neck and bladder. This allowed the creation of an angle at the posterior bladder neck. It required complete separation of the bladder from the urethra and a reanastomosis of the neourethra to the native urethra. (a) The bladder outlet is divided from the urethra and an anterior bladder-based tube is formed. (b) The flap is tubularized. (c) The posterior bladder is closed. (d) The tube is sewn to the urethra.

Bladder Neck Closure

The ultimate bladder neck reconfiguration is complete closure of the bladder outlet. Today, after years of experience, we feel that most, but not all, bladder necks can be made continent. Those that cannot be repaired can be closed. The concept of bladder neck closure was made a viable option in 1980 when Paul Mitrofanoff constructed the continent appendicovesicostomy and combined it with bladder neck closure in patients with neurogenic bladder (Figure 56.22).[124] Duckett and Snyder presented variations of bladder neck closure and continent stomas, and Van Savage et al. presented a series of 46 children with closure of bladder neck.[125,126]

In general, bladder neck closure is a procedure of last resort and is utilized after other more flexible options in bladder neck reconstruction have been exhausted.[127,128] The indications for bladder neck closure are intractable urinary incontinence resistant to maximal medical management and reasonable surgical management. Patients usually have failed previous incontinence surgery or suffer from a primary condition that projects failure. The obvious advantage is complete urethral continence in as many as 96% of patients. Eighty-nine percent have stable upper urinary tracts, and no bladder capacity is lost in the creation of a continence mechanism.[129] Disadvantages include a complete lifelong reliance on an extra-anatomic method of bladder emptying and no pressure pop-off valve. Bladder neck closure does have complications, with one series reporting initial results of 20% with stomal incontinence and 40% with urethral fistulas and persistent urethral leakage.[130] With surgical revision, 85% became completely continent. In reviewing multiple reports, 65% of patients with closed bladder necks require additional surgery for complications, such as fistulas, stones, augmentation, ruptures, and other revisions.

The Mitrofanoff Principle

Mitrofanoff's contribution, now termed the Mitrofanoff principle, has had a profound effect on incontinence surgery in children. His development of alternative continent bladder access through a continent stoma has relieved the necessity for the patient to either void efficiently or catheterize through the reconstructed bladder neck. There have been other alternatives to Mitrofanoff's original use of appendix for extra-anatomic access to the bladder. Other options for continent bladder access include

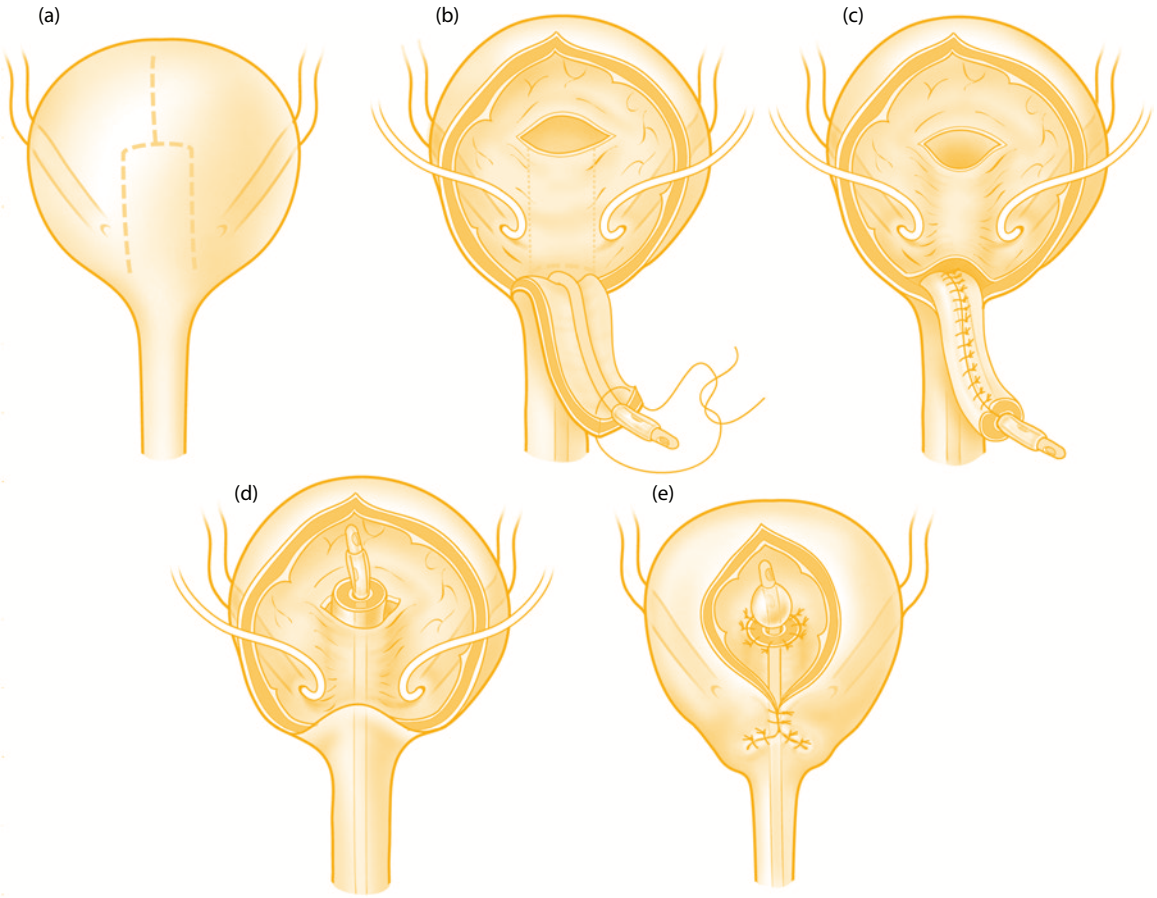

FIGURE 56.19 Kropp also creates a neourethra from a flap of anterior bladder neck and bladder, but unlike Tanagho, Kropp's flap is based on the urethra. The flap is tubularized and then placed in a submucosal tunnel created along the midline of the posterior bladder wall. (a) An anterior urethral-based flap is mobilized. (b and c) The flap is tubularized. A submucosal tunnel is made in the posterior bladder wall. (d and e) The tube is placed in the tunnel.

the ureter, fallopian tube, bladder tubes, and tubularized bowel.[131–133] With the recent interest in the Malone antegrade continence enema (MACE) for patients with neuropathic bowel and bladder, the appendix has been used more often as access to the colon.[134]

Tubularized ileum and Yang–Monti tubes have been the most dependable and flexible method of bladder access for these patients (Figure 56.23).[135] We have developed a longer ileal tube for patients with a greater distance between the bladder and skin (Figure 56.24).[136] Today, an easily accessible, continent, catheterizable access for emptying the bladder is available for almost all patients.

We believe that catheterizable abdominal stomas promote continence by avoiding manipulation of the reconstructed bladder neck. In some cases, they encourage patient compliance with intermittent catheterization because catheterizing through an abdominal stoma is easier and less time-consuming than urethral catheterization for many patients. Regular catheterization keeps bladder pressures low and minimizes stress on reconstruction done at the bladder neck. Stomas allow the surgeon to be more aggressive in creating resistance at the bladder outlet because the urethra will not be needed as the primary access for catheterization. The combination of continent stomas and augmentation has allowed patients who have suffered multiple failed continence surgeries to be salvaged with good results.[137]

INDICATORS FOR SUCCESS

The definition of continence has changed over the years and is open to interpretation by each surgeon.

"Social continence" was felt to be adequate in the past, and if a child used several continence pads per day but was free of diapers, most pediatric urologists considered their treatment successful. Our tolerance of wetness has been modified over the years, perhaps in response to the change in public policy in the 1970s to mainstream the education of children with disabilities. In more modern reviews, surgeons have been more specific in defining successful continence. Dryness, without the odor of urine, has become the expected goal. This evolution of the definition of success makes comparing results from different eras and series difficult.

The effectiveness of procedures to treat the weak bladder outlet cannot be judged easily. Ultimate success is of course based on continence, but also involves other criteria, such as the ability to void and the need for other surgery to attain continence, such as bladder augmentation.

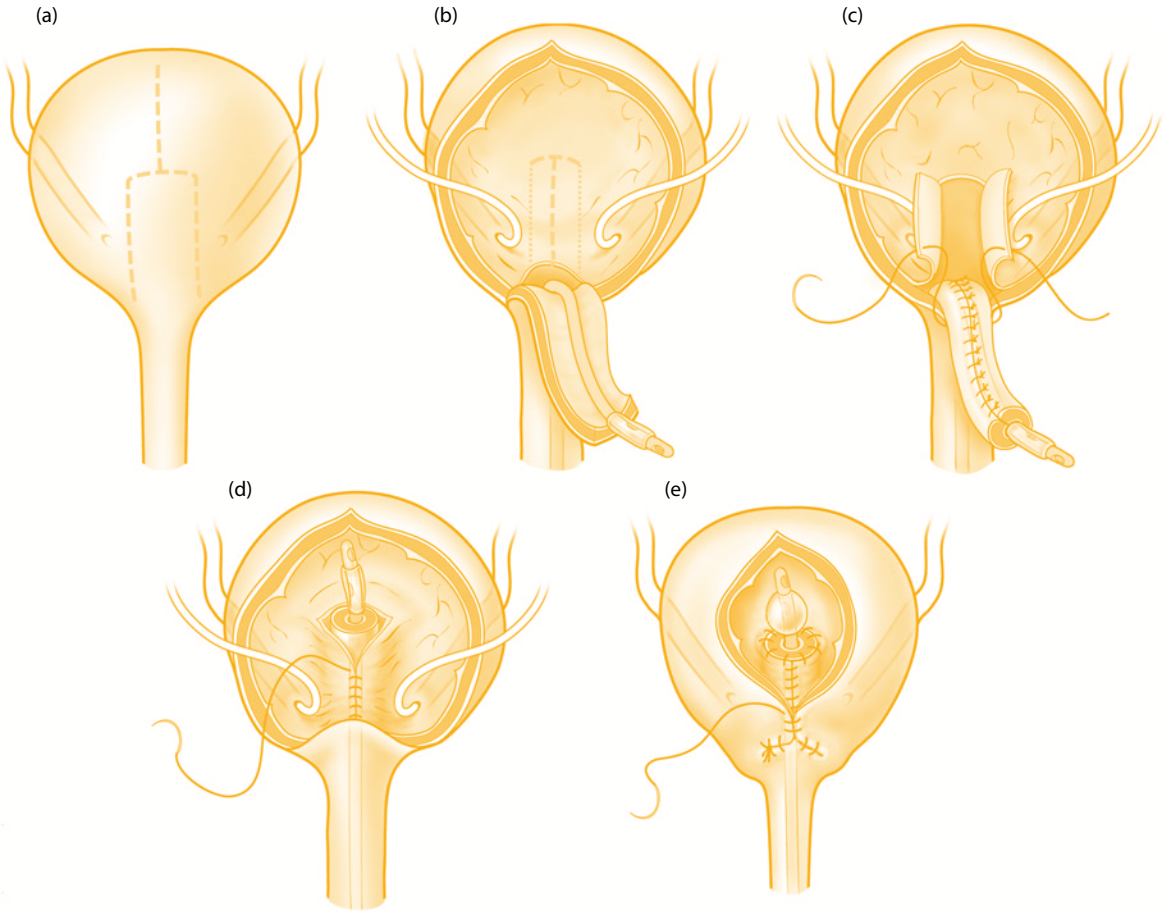

FIGURE 56.20 The Snodgrass variation of the Kropp procedure lays the Kropp tube in a trough instead of a tunnel. Construction of the tube is identical to that of Kropp. (a) A full thickness flap of bladder is isolated from the anterior bladder wall and encompasses the bladder neck. (b) With the anterior flap rotated out of the way an incision is made in midline of the bladder mucosa. (c) The anterior bladder flap is rolled into a tube in continuity with the proximal urethra. Mucosa is mobilized on either side of the midline incision exposing a trough in which the anterior bladder tube will rest. (d) The bladder tube is sewn into the trough and then covered with the bladder mucosa flaps creating a flap valve for continence in patients who are committed to intermittent catheterization. (e) The bladder is closed.

It is unfair to compare procedures that allow voiding with those that prevent voiding by design.

Of the procedures that allow voiding, the YDL procedure, its variations, and the Tanagho repair have been the most successful, allowing 70%–100% of patients to void initially. Voiding after this type of surgery is seldom normal, for these procedures usually produce a fixed resistance at the weak bladder neck. Voiding is often accomplished with abnormally high bladder pressures that are generated by Valsalva's maneuver. These pressures are necessary to overcome the static-increased bladder outlet resistance. Even if the patient is able to void for a period of several years, the detrusor may eventually fail and require intermittent catheterization. Many procedures produce 75% continence rates, but often these rates are dependent on intermittent catheterization and chronic detrusor relaxation achieved with medication or augmentation.

The artificial urinary sphincter would seem to be the best alternative for the patient who can void prior to surgery, as it provides a variable resistance at the bladder neck and should allow voiding at more physiologic pressures. Long-term studies of sphincters in children reveal that most patients eventually require intermittent catheterization because of inadequate emptying due to detrusor failure. The other complications of inevitable reoperation and potential secondary detrusor hyperreflexia are additional considerations with this device. If the patient does have the potential to void over a long period of time, the artificial sphincter is the best option. Around 80% of patients will be continent over a long period of time with the sphincter, although most require intermittent catheterization. Augmentation rates of 30%–35% in long-term selective studies are less than those with other bladder procedures.

Of the procedures that prevent voiding by design and rely on intermittent catheterization, the slings are the most simple and dependable in females and produce 80% continence rates with good durability. The Pippi Salle bladder neck reconstruction produces 80% continence, whereas the Kropp procedure produces the highest continence rates, approaching 100%. Bladder neck closure is also very dependable but leaves the patient reliant on only one bladder access, an extra-anatomic continent stoma, and no pop-off valve.

If one is choosing a bladder neck procedure, one must have specific goals in mind relating to the patient's potential to void. Patients with neuropathic bladders from sacral agenesis, myelomeningocele, and spinal cord trauma have poor potential to void regardless of bladder outlet resistance. Patients with

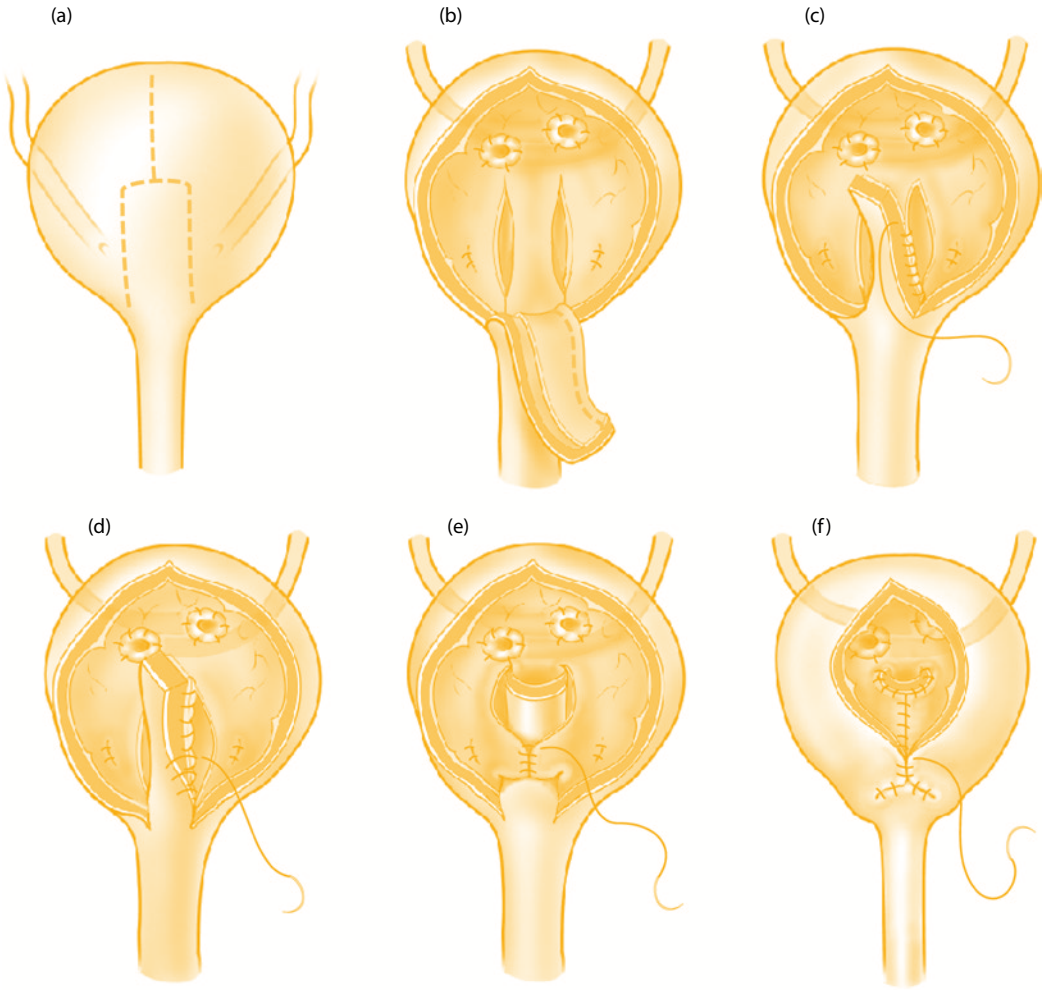

FIGURE 56.21 Pippi Salle creates a neourethra from an anterior and a posterior strip of bladder neck and bladder. The two are sewn together, but only the anterior flap is mobilized completely. The posterior flap is isolated but not mobilized from the posterior bladder wall. The neourethra is then covered with mucosa and some muscle, which is mobilized on each side. (a) An anterior bladder flap is mobilized. (b) A posterior bladder mucosal flap is mobilized. (c) The mucosas of the anterior and posterior flaps are sewn together. (d) The muscles of the flaps are sewn together. (e and f) The bladder mucosa is closed over the neourethra.

epispadias and some with exstrophy have better detrusor function as a group and have the best potential to void.

If the goals of surgery are to have the patient dry and voiding, the artificial sphincter would seem the best choice, followed by the YDL procedure or variations. If the surgical goals are to have the patient dry and to catheterize through the bladder neck and urethra, the Pippi Salle repair or the artificial sphincter allows continence with easy catheterization in most cases. If the goals are to have the patient dry and the bladder neck and urethra are not important for voiding or catheterization because a continent stoma is available, then the Kropp repair and a bladder neck closure are good options.

Another measure of success that has been used to judge bladder neck surgery is the need for bladder augmentation to achieve continence. On the surface, it would seem that the YDL procedure and its variations and the Tanagho procedures are superior because series of these procedures report augmentation rates of 0%–40%. This compares with Kropp's reported augmentation rate of 78%, bladder neck closure of 61%–80%, and Pippi Salle repair rates of 80%. Closer inspections of the series reveal that the patient groups are not comparable. Studies with the lowest augmentation rates (15%–20%) are consistently made up of mostly epispadias, exstrophy, and urogenital sinus patients, whereas the series with high augmentation rates (70%–90%) usually include a significant number of neuropathic bladders. The need for augmentation is much more a function of the underlying condition and the pathophysiology of the detrusor rather than a result of bladder outlet incompetence or corrective surgery.

CONCLUSIONS AND RECOMMENDATIONS

Patients found to have incontinence due to bladder outlet incompetence as demonstrated by leak point pressures, cystograms, or cystoscopic examinations should always be treated with all available medical options needed to improve continence. CIC, anticholinergic medication, α-adrenergic medications, control of constipation, and

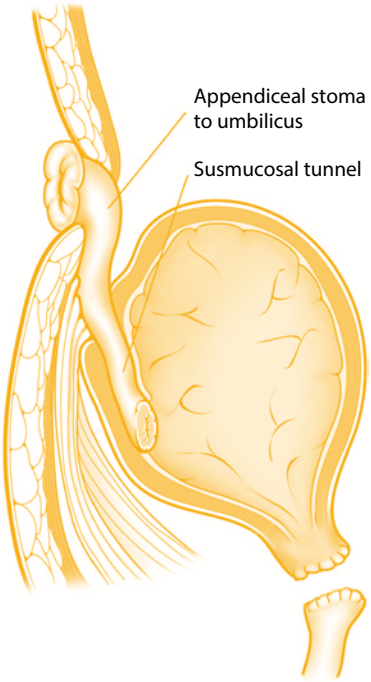

FIGURE 56.22 Mitrofanoff used a continent catheterizable stoma to empty the bladder. By implanting the appendix into the bladder in a continent manner, he allowed efficient bladder emptying without relying on the urethra. This allowed him to close the bladder neck surgically, leaving the appendix as the only access with which to empty the bladder.

control of infection should be utilized. If these methods fail and the patient and family have the sufficient motivation and understanding of what continence procedures require, then the urologist may explore the surgical options.

The patient and family should have a vital role in the decision-making process, and they must understand the consequences of having surgery to increase leak point pressure. The surgeon makes a profound change in the physiology of the urinary tract and, in doing so, depends on the patient and family to perform the management required by this change. Whether it is performing intermittent catheterization, emptying the bladder on schedule with an artificial sphincter, or taking medication, the success of the surgery and the health of the child depend on their willingness and ability to comply.

Once the child, family, and surgeon agree to perform a procedure to increase resistance at the bladder neck, there are many good options. The choice of procedure depends on the goals of surgery and the particular surgeon's preferences. It is important to approach each patient individually. Children with incontinence that requires surgical management are often complex cases, with other health and social concerns. In general, however, we can look at the underlying pathology and goals of surgery and recommend procedures that are good management options.

If the child can void to completion prior to surgery and has a condition that may allow long-term voiding, then the artificial sphincter or the YDL procedure is a good option. The conditions that leave children with relatively isolated bladder outlet incompetence and adequate detrusor function include epispadias, bilateral ectopic ureters,

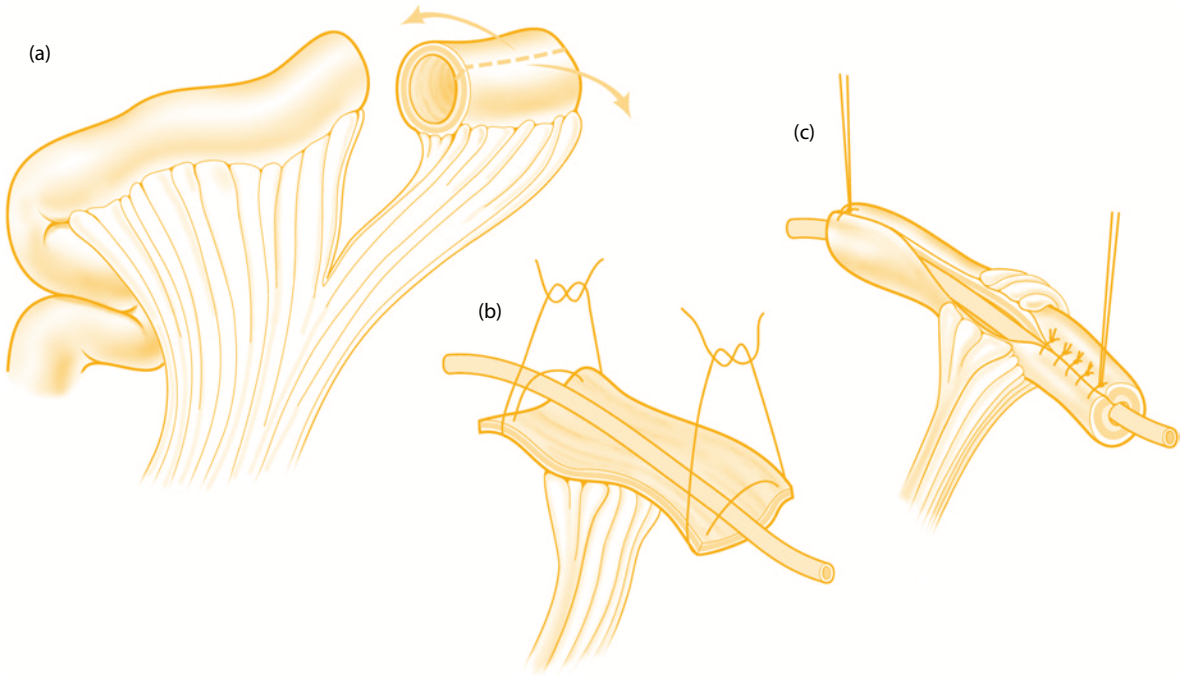

FIGURE 56.23 Monti popularized a concept originally described by Yang, who created a catheterizable tube from small bowel. (a) A 3–4 cm section of bowel is isolated on its mesentery and split on the antimesenteric border. (b) It is then closed along the transverse axis, 90° from the original. (c) This doubles the length of tube produced from a piece of bowel. The tube may then be implanted into the bladder for continent catheterizable access.

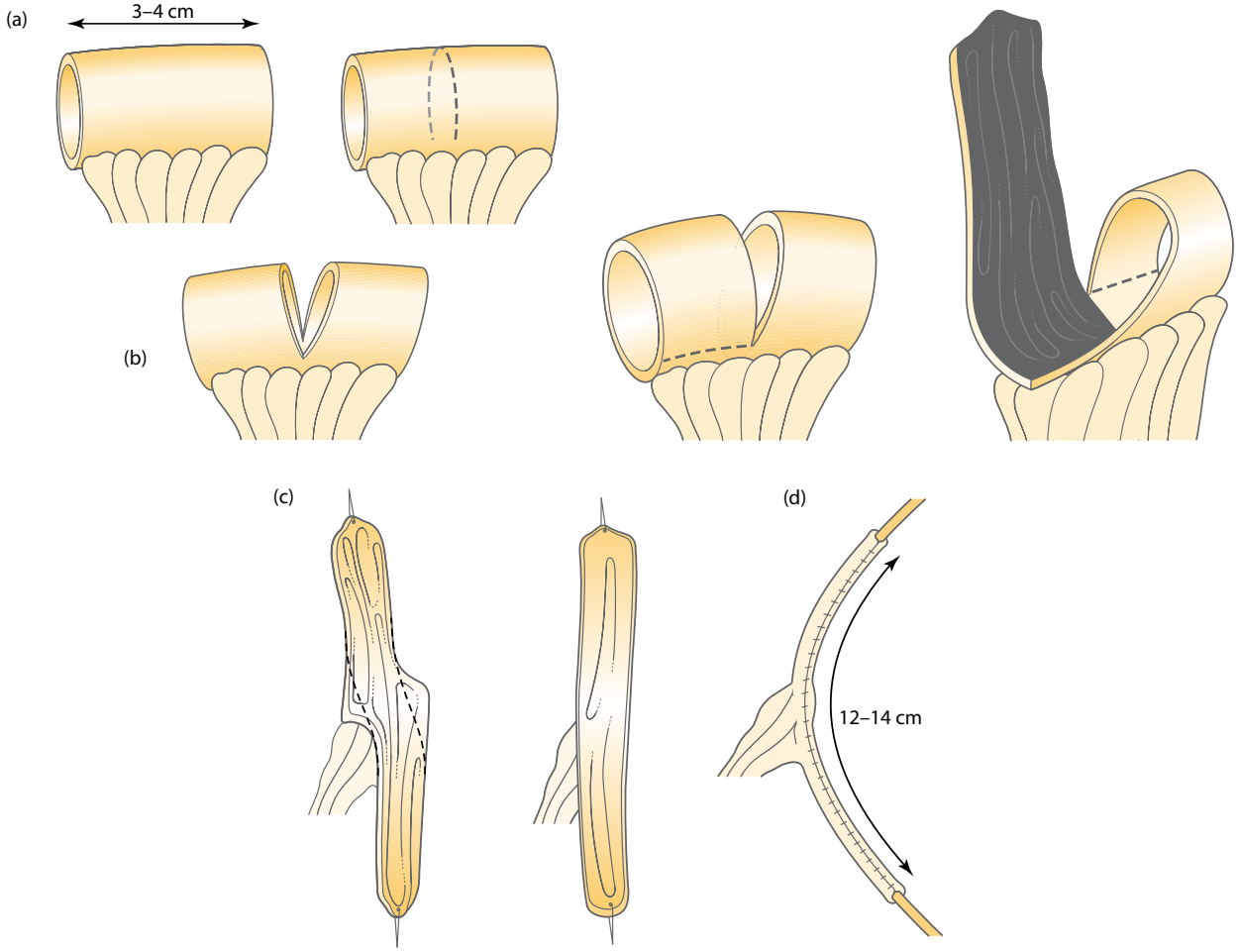

FIGURE 56.24 Casale presented a variation of the reconfigured ileal tube. (a) A 3–4 cm section of ileum is partially split into two rings, leaving the bowel over the mesentery intact. (b) The two rings are then split on opposite sides, allowing the bowel to be unfolded into a much longer flap. (c) Corners of bowel along the mesentery are trimmed off to make the strip uniform in width before it is tubularized. (d) The longer tube allows more flexibility in placement of the anastomosis, mesentery, and stoma.

some surgical injuries to the bladder neck, and urogenital sinus anomalies. As a rule, artificial sphincters should not be used if there has been prior bladder neck reconstruction, such as in exstrophy closure, because of the risk of erosion. The rare child with pure stress incontinence may be treated with suspension of the bladder outlet using any of the procedures used in adult stress incontinence, such as the McGuire or Raz procedures. Slings may be used in children who void, but they should be applied loosely.

Patients with exstrophy are still treated with the YDL procedure or one of the variations. New urodynamic data suggest that procedures such as the YDL procedure, which surgically alter the trigone, may lead to worsening of detrusor function. Kaefer et al.[138] studied epispadias patients and Diamond et al.[139] reviewed exstrophy patients before and after bladder neck surgery, and both studies showed that most patients suffer a deterioration of filling and voiding dynamics. Most bladders developed high pressures, increased contractility, and diminished capacity, whereas some bladders increased in size and developed poor contractility. Only 25% of 30 exstrophy patients maintained normal detrusor function after their bladder outlet resistance was surgically increased. We have yet to determine whether the detrusor functional changes observed are the result of surgical trauma to the bladder or increased demands on the bladder to retain urine and cycle, or are predetermined by different levels of dysfunction inherent in each exstrophy bladder.

The newest development in exstrophy surgery is to perform the entire repair, including closure, bladder neck reconfiguration, and urethroplasty, as a single procedure in the newborn period.[140] Multiple reports have shown that while complete primary repair of exstrophy can be successful, many patients need additional bladder neck reconstruction to attain continence, and there are potential complications that are less common in staged repairs in some surgeon's hands.[141]

At the time of bladder neck repair, it has been our practice to add a continent umbilical urinary stoma.[142,143] This allows the child to void per urethra and also offers easy access to check residual urine or to perform intermittent catheterization without violating the repaired bladder outlet if the child cannot void adequately. We believe that the surgeon should elevate and suspend the bladder neck and urethra at the same time as a bladder outlet reconfiguration, such as the YDL procedure, is performed.

In patients who cannot void adequately prior to surgery and who have poor potential for good detrusor function,

there are more options. These children, for the most part, have neuropathic bladders from myelodysplasia or other neurologic conditions. They will be dependent on CIC to empty the bladder. In girls, the fascial sling has become the treatment of choice because of its simplicity and reliability. In boys, there are many options, but we currently use the YDL, Pippi Salle, or Kropp procedures. If the plan calls for intermittent catheterization through the repaired bladder neck in a boy, the Pippi Salle procedure is preferred because it is easy to catheterize. At this time, almost all patients have the simultaneous creation of a continent catheterizable abdominal stoma. This allows easy access to the bladder, and there is no need to worry about routine catheterization or catheter trauma to the repaired bladder outlet.

The majority of children with neuropathic incontinence at the bladder outlet also have bladders with limited detrusor function and storage capacity. Most children today undergo a simultaneous augmentation cystoplasty to create a large, low-pressure storage reservoir. There is no question that augmentation alone will improve continence in this patient population even if the bladder outlet is weak.[144] In our experience, augmentation alone has not provided reliable continence even in patients with reasonable bladder outlet resistance. For this reason, we believe that in most cases of reconstruction for incontinence, the surgeon should maximize both bladder outlet resistance and the storage capacity of the bladder.

In writing the second revision of this chapter, I again am impressed by the change in emphasis on surgical treatment of severe anatomic and neuropathic incontinence. Many factors are at work here, including years of less than perfect results and a drop in the number of new patients with these conditions due to in utero diagnosis and termination, along with the effects of folic acid supplements. It is also a fact that pediatric urologists do less open surgery, especially around the bladder, and our residents and fellows have less experience in training.

New work in this field is directed toward less aggressive surgical intervention, such as slings, wraps, and injection therapy. There have been few advances in the area of major bladder outlet reconstruction in the past 8 years, and if anything, this surgery has become less radical, as in the modifications of the YDL procedure.

Procedures to improve resistance at the incompetent bladder outlet have been advanced greatly by the development of associated procedures, such as bladder augmentation over the past 25 years. Two singular contributions in this field came from Lapides, with his concept of CIC, and Mitrofanoff, whose novel idea to create a continent catheterizable stoma allowed a nonurethral method of bladder emptying. Finally, the predictors of success in bladder outlet reconstruction remain unchanged despite any new advances. They are sufficient resistance at the bladder outlet, a low-pressure reservoir of adequate size, and a reliable means to empty the bladder efficiently.

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CHAPTER 57

Bladder Augmentation: Current and Future Techniques

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INTRODUCTION

The surgical management of the child with a neuropathic bladder can be a formidable task, but major advances in surgical technique have been made in recent decades. The ability to augment the capacity of the bladder with a piece of reconfigured bowel, in conjunction with clean intermittent catheterization (CIC), has dramatically altered our ability to form a compliant urinary reservoir that protects the integrity of the upper urinary tract and promotes urinary continence. Conventional enterocystoplasty uses detubularized segments of small or large bowel. Despite the functional success of intestinocystoplasty, clinical experience has demonstrated that numerous complications can result from the incorporation of small and large bowel and their associated heterotopic epithelium into the urinary tract. To avoid some of these deleterious side effects of the use of bowel for bladder augmentation, several procedures have now been developed to augment the bladder without the use of bowel, including gastrocystoplasty, autoaugmentation, seromuscular enterocystoplasty, and ureterocystoplasty. In addition, recent advances in tissue engineering techniques have increased the possibility of regenerating new bladder tissue that is clinically useful for augmentation purposes. This chapter reviews the relevant surgical anatomy and physiology, advantages and disadvantages, surgical techniques, and clinical results of conventional enterocystoplasty and each of the alternative procedures that avoid the use of bowel. These are summarized in Table 57.1. Since the care of the child with a neuropathic bladder can be complex and requires individualization that is dependent on the desires of the patient and family, familiarity with each of these procedures is extremely important for the pediatric urologist when considering augmentation cystoplasty.

Many different surgical techniques have been developed over the years by many dedicated surgeons aiming to increase the health and life quality of their patients. Not every technique is suitable for every patient, and careful selection is necessary to avoid failure and reoperations, frustrating for patients, families, and surgeons alike. Every new approach aims to minimize complications of previous techniques while improving or at least achieving the same functional outcome. In order to avoid complications, conservative and minimal invasive therapies have been developed with mixed results. However, bladder augmentation using intestinal segments, with all its problems, still has the most durable long-term functional outcomes and possibly satisfaction rates. The authors of this chapter recommend careful study of the various described procedures in order to allow the surgeon to choose the best-fitting procedure for an individual patient.

INDICATIONS AND PREOPERATIVE ASSESSMENT

Enterocystoplasty is performed when there is a need to enlarge and/or decrease the storage pressure in the native bladder, when the native bladder becomes an inadequate reservoir owing to abnormal bladder wall dynamics. This can result from a host of conditions, including spina bifida, spinal cord trauma, posterior urethral valves (PUVs), dysfunctional voiding, radiation, and infectious or other chronic inflammatory processes. Wiener et al. reported that 3403 patients with spina bifida received enterocystoplasty between 1998 and 2005. During that same time period, 772 ileal loop diversions were performed in spina bifida patients. Their data demonstrated that younger male patients with private insurance were more likely to have an enterocystoplasty than urinary diversion.[1] Enterocystoplasty is intended to relieve high-pressure and low-capacity characteristics. There are two major indications for enterocystoplasty. The first is the presence or risk of upper tract deterioration secondary to a poorly compliant bladder. The second indication is when the bladder is a causative factor in urinary incontinence. All patients who are being considered for enterocystoplasty should be thoroughly studied with preoperative urodynamics and initially treated by medical alternatives, such as anticholinergic medications and/or intermittent catheterization. It is extremely important that patients understand that, in most instances, enterocystoplasty will not result in normal voiding and a lifelong commitment to intermittent catheterization will be required.[2]

Lapides's landmark studies in the early 1970s, demonstrating that intermittent catheterization can be performed safely and effectively in children,[3,4] have had the

TABLE 57.1 Advantages and disadvantages of procedures for bladder augmentation

Procedure	Advantages	Disadvantages
Intestinocystoplasty	Extremely compliant tissue Availability of tissue Proven long-term clinical efficacy	Heterotopic epithelium Mucus Infections Stones Hyperchloremic metabolic acidosis Malignant transformation Spontaneous rupture
Gastrocystoplasty	Moderately compliant tissue Easily definable submucosal plane for reimplantation Minimal mucus and stone formation Acid buffering in renal insufficiency patients	Hematuria dysuria Hypochloremic hypokalemic metabolic alkalosis
Autoaugmentation	Preservation of native urothelium Avoids bowel Technically less demanding procedure Extraperitoneal procedure Does not preclude future conventional enterocystoplasty	Inability to predict success preoperatively
Seromuscular enterocystoplasty	Preservation of native urothelium Muscle-backed mucosa	Technically more demanding procedure Factors that predict success preoperatively not well defined
Ureterocystoplasty	Preservation of native urothelium Muscle-backed mucosa Compliant tissue Avoids bowel	Limited patient population Large surgical incisions

single greatest impact on the ability to perform enterocystoplasties in children. If a patient is not dedicated to performing lifelong intermittent catheterization, then a noncontinent form of urinary diversion should be chosen instead of enterocystoplasty.

The goals of enterocystoplasty are to change the native bladder environment by reducing storage pressure and increasing volume. A thorough preoperative evaluation will help to determine which type of augmentation is most appropriate and beneficial for each child. Major factors that must be addressed before proceeding with enterocystoplasty include (1) assessment of renal function, (2) absence or presence of reflux and/or ureteral dilatation, (3) determination of outlet resistance, (4) history of bowel dysfunction, (5) need for a continent catheterizable stoma, (6) physical and mental capacity to perform intermittent catheterization, and (7) previous urinary diversion. Since there is currently no perfect bladder augmentation applicable to all children, all the above factors must be considered in order to make the most suitable and best choice for the patient and his or her family.

Renal Function

Renal function can be assessed by measurement of serum creatinine, using one of several methods to calculate estimated creatinine clearance; 24-hour urine collection; or estimation of the glomerular filtration rate via a radioisotope renal scan. The authors prefer to obtain a serum creatinine and nuclear renal scan before any type of bladder augmentation if the renal ultrasound is abnormal. The information obtained from this assessment may make one segment of bowel or an alternative procedure more attractive or appropriate than others. For example, in a patient with chronic renal insufficiency, a gastrocystoplasty is often a better choice than intestinocystoplasty because fewer urinary wastes are absorbed and electrolyte disturbances, such as metabolic acidosis, are reduced.

Reflux and Ureteral Dilatation

The presence of reflux and/or massive ureteral dilatation is an important preoperative determinant. When massive ureteral reflux is present, the exact bladder capacity and compliance may be difficult to assess. Occlusion of the ureteral orifices with balloon catheters can be helpful in assessing these parameters. An anesthetic is usually required to place these catheters. Although this technique has been reported, the authors have not found this procedure to be very helpful and therefore rarely perform it.

Reflux has been reported to resolve spontaneously after enterocystoplasty.[5–8] Antireflux surgery should be considered at the time of reconstruction, especially if reflux occurs at low intravesical pressures. In patients who have low- to moderate-grade reflux in association with high intravesical pressures and poor bladder compliance, enterocystoplasty alone, without ureteral reimplantation, can be considered, as the reflux tends to resolve with reduction of intravesical pressure. Recently, endoscopic subureteric injection with dextranomer/hyaluronic acid copolymer has been shown to correct reflux with a high degree of success. Thus, in cases of mild to moderate reflux that occurs at elevated pressures, the authors are more likely to proceed with augmentation without concomitant open reimplant surgery. If the reflux does not

resolve after augmentation, then endoscopic correction can be performed. Alternatively, endoscopic correction can be considered at the time of augmentation, especially in cases where concomitant bladder neck procedures that may limit endoscopic access are being performed.

In patients where there is ureteral dilatation in the absence of reflux, a very low-pressure reservoir must be constructed so that adynamic ureters can propel the urine into the bladder. Although not well documented in the literature, clinical experience strongly suggests that dilated ureters with walls that do not coapt are not capable of generating a peristaltic wave of greater than 40 cmH_2O. Thus, dilated ureters are likely to require very low intravesical pressures, well below 40 cmH_2O, for proper efflux of urine into the bladder.

Preoperative assessment of native bladder wall dynamics can be extremely difficult in patients who have a neuropathic bladder with an open bladder neck and low outlet resistance. In these patients who leak from an empty bladder, cyclical filling and distension of the bladder do not occur. The bladder has not been stretched under physiologic conditions. When performing preoperative urodynamics in these patients, a balloon catheter can be snugged down into the bladder neck to prevent leakage and bladder capacity, and compliance can be evaluated. This technique has been reported to be a good predictor of the need for future augmentation.[9] However, Kronner et al.[10] demonstrated that preoperative urodynamics in such patients do not necessarily correlate well with eventual bladder outcome. They concluded that preoperative assessment of bladder capacity and compliance could not reliably predict which patients would eventually require enterocystoplasty after outlet resistance had been increased. Since preoperative urodynamics do not appear to be accurate in patients with an open bladder neck, the decision to perform an enterocystoplasty in conjunction with a bladder neck procedure should be based on preoperative discussions regarding the risks and benefits of immediate versus delayed enterocystoplasty.

Previous Urinary Diversion

As with patients with low outlet resistance, those with a defunctionalized bladder secondary to previous urinary diversion who are being considered for undiversion or transplantation are also difficult to assess preoperatively with regard to the need for bladder augmentation. In patients with a vesicostomy, urodynamics can be performed by occluding the vesicostomy with the balloon from the urodynamic catheter. For the same reasons previously described for patients with a poor outlet, interpretation of these urodynamic findings and assessment of their significance may be difficult. In PUV patients who have previously had urinary diversion and subsequently undergo renal transplantation, there are good data showing that the native bladders reexpand and regain function irrespective of preoperative urodynamic findings.[11–13] Currently, there are few data on outcomes in patients with neuropathic bladders associated with spina bifida after primary closure or undiversion without enterocystoplasty.

In the defunctionalized bladder not associated with spina bifida, some authors feel that bladder cycling may help to determine whether a bladder is adequate for closure without augmentation.[12,13] A gastrotomy button placed in the vesicostomy to facilitate bladder cycling can be used in these patients.[14] The authors' experience has been that preoperative bladder cycling can be helpful in some patients, at least in increasing bladder capacity. However, urodynamic results remain difficult to interpret in many. In general, we favor undiversion without augmentation when there is doubt as to whether augmentation will be required. Secondary enterocystoplasty can always be performed in patients in whom the bladder does not eventually attain adequate bladder compliance and capacity following undiversion or transplantation. It should be emphasized that this approach is only recommended for patients with a defunctionalized bladder not associated with spina bifida, since such patients usually do poorly following vesicostomy closure. Reliable follow-up also needs to be ensured in all patients following undiversion.

Bowel Function

A thorough evaluation of bowel function, including a history of constipation or diarrhea, must be carried out prior to enterocystoplasty. Postoperative bowel dysfunction can occur in up to 50% of patients who have undergone enterocystoplasty.[15] In addition, King[16] found that removal of the ileocecal segment in children with spina bifida causes severe diarrhea in approximately 10% of patients. However, in a more recent series of 63 patients who underwent ileal cecal cystoplasty, bowel complication was found to be only 3%.[17] Nevertheless, before undertaking any type of urinary reconstruction that involves the use of a bowel segment, discussion with the patient and family should include potential gastrointestinal complications. The type of augmentation should be chosen with these potential complications in mind.

Ability to Catheterize

Since most patients who undergo enterocystoplasty will not be able to void completely and will require lifelong intermittent catheterization, one should consider the formation of a catheterizable stoma at the time of the augmentation. This is especially important in patients who are sensate or are in wheelchairs. Clinical experience has shown that when both the native urethra and a catheterizable stoma are present, the majority of patients will choose to use the catheterizable stoma. In addition, assessment of the physical and mental capacities of the patient and family must be undertaken to make sure that they will be able to perform intermittent catheterization on a regular schedule.

Families want to believe that their child will become continent after enterocystoplasty and that the kidneys will be protected. However, the amount of time and effort that will be required is often not appreciated preoperatively. Therefore, all must understand the risks and benefits of enterocystoplasty prior to surgery and the lifelong commitment to a relatively rigorous schedule of intermittent catheterization. Since there are many potential problems associated with failure to catheterize, including spontaneous bladder rupture and death, urinary reconstruction

should be deferred until the patient has the physical and mental maturity needed to care for himself or herself.

Alternative Therapies

Botulinum Toxin

The intravesical injection of botulinum toxin (Botox) is a good temporary measure to enhance bladder capacity and decrease intravesical pressures.[18] Botox is injected into the detrusor muscle endoscopically using a cystoscope under anesthesia. It is generally very well tolerated, and the effects last for several months. The procedure is, however, not Food and Drug Administration (FDA) approved. Botox injection can be repeated safely, but due to its temporary effect, it is not a final measure and will possibly require additional procedures later.[19]

Transurethral Electrical Bladder Stimulation

The technique begins with detailed bladder capacity measurements, followed by refilling the bladder via an electrocatheter. Various electric parameters, such as intensity of current and frequency, can be adjusted to the individual patient. Bladder stimulation therapy will provide volitional voiding in less than 10% of patients but can be an effective form of treatment for up to 60% of patients. The beneficial effects are generally permanent, but the therapy is very labor-intensive and requires a very dedicated family.[20]

Sacral Neuromodulation

Sacral neuromodulation (InterStim) can improve bladder function either by consistent stimulation of the efferent fibers of the sacral nerve roots or by providing rhythmic contractions of the pelvic floor.[21] The device consists of a pacemaker, placed in the area of the buttocks, and a neurostimulator lead that is tunneled under the skin to electrically stimulate the S3 nerve root. A prospective, randomized study enrolled 42 patients with spina bifida and compared urodynamic outcomes and incontinence. The implanted group demonstrated significantly improved leak point pressures.[22] Further studies will be necessary to evaluate the true advantage for patients with spina bifida.

Xiao Procedure

The Xiao procedure is a neurosurgical technique in which a new neuronal loop is created unilaterally between the ventral roots of L5 and S3. The originators of this method first reported their successes in spinal cord–injured adults, showing that via percutaneous electrical stimulation or scratching of a skin dermatome, a detrusor contraction could be initiated with promising results in increased bladder control.[23,24] A study in the spina bifida population of 20 children demonstrated 17 (85%) with increased bladder storage capacity and emptying functions. This included the ability to sense fullness and to initiate bladder emptying with L5 dermatome stimulation and eventually achieving dryness after 6 months. However, 5 of the 17 children with bladder success also had signs of partial loss of L5 motor function. In the three patients who had no improvement, two were noted to have significant scarring in the spinal canal due to their previous surgeries, and therefore had inadequate neural rootlet identification.[25] In 2010, Peters et al. published their 1 year results in the first U.S. trial on nine patients. Most patients had an improvement in bowel function, but none achieved complete urinary continence. Two patients could stop CIC, and antimuscarin medication was safely stopped in all. Temporary weakness of lower extremity muscle groups occurred in 89%, and one child had persistent foot drop. The authors concluded that more patients with longer follow-up are needed before the procedure can be universally recommended.[26] To our knowledge, only two centers in the United States, one in Detroit and one in Tampa, are currently offering the procedure.

Bladder Neck Procedures

The bladder neck can either be competent or have little resistance, requiring a bladder neck procedure to avoid postoperative urine leakage. Bladder neck procedures aim to tighten the bladder outlet either by creating a muscular channel or by placing a sling to tighten and elevate the bladder neck region. Both procedures create a controlled obstruction to prevent urine flow under low pressures but allow urine leakage if the intravesical pressures become too high. Since most patients do not have an adequate native bladder, providing them with a sufficient, low-pressure-reservoir simultaneous bladder augmentation is often necessary. However, Snodgrass and Barber reported the possibility of performing a bladder neck procedure without augmentation.[27] The group observed that in their patients, the bladder usually will eventually gain enough compliance to prevent unsafe intravesical pressures that could harm the upper tracts. As with all major congenital conditions, various management protocols exist and are defended by their proponents compassionately. These controversies and educated discussions are highly desirable since they spark more research and advance the field.

INTESTINOCYSTOPLASTY

Small Bowel

Currently, ileum is the most commonly used bowel segment for enterocystoplasty. The abundant supply of small bowel, easy workability, mobility, reliable blood supply, and compliance of the reconfigured ileum have led most reconstructive surgeons to choose ileum over other bowel segments. Although the jejunum can be used for urinary reconstruction, the high incidence of metabolic complications (hyponatremic, hypochloremic, and hyperkalemic acidosis) associated with use of this segment makes it less desirable, and thus it is rarely used. The major contraindications to the use of ileum are a history of short gut syndrome, inflammatory bowel disease, pelvic and/or abdominal radiation, and significant renal insufficiency. Under these conditions, alternative segments, such as the stomach, are more appropriate.

Anatomy and Physiology

The proximal two-fifths of the small bowel proper is jejunum, and the distal three-fifths is ileum. The coils of the midileum usually lie in the pelvis, while the terminal 30 cm of the ileum, the most commonly used portion for

enterocystoplasty, usually rises out of the pelvis to lie in close relationship to the cecum and the ascending colon.

The mesentery of the small bowel attaches to the posterior abdominal wall. The "root" of the small bowel mesentery runs obliquely across the abdomen. As the root of the mesentery runs obliquely from left to right, it crosses, in order, the abdominal aorta, the vertebral column, and the third portion of the duodenum. The midportion of the small bowel has the longest mesentery, whereas the segments of the small bowel closest to the cecum and the duodenojejunal flexure have the shortest. Therefore, in patients in whom the mesentery is short, a segment of ileum 30 cm or more above the ileocecal valve will be the most mobile and will reach the furthest into the pelvis.

The arterial supply to the entire small bowel is derived from the superior mesenteric artery (Figure 57.1). There are usually 12–16 branches of the superior mesenteric artery running to the jejunum and ileum and entering the small bowel at its mesenteric border. The ileocolic artery is the most distal segment of this vessel. It is found in the right lower abdominal quadrant, where it gives off branches that supply the terminal ileum, the cecum and appendix, and the proximal ascending colon. Venous drainage of the small bowel occurs through multiple mesenteric channels that coalesce to form the superior mesenteric vein. It is this abundant and redundant blood supply that makes the use of different segments of ileum available for urinary reconstruction.

The small intestine is innervated from the autonomic plexuses grouped around the "takeoff" of the superior mesenteric artery from the aorta. These plexuses include preganglionic parasympathetic nerves from the vagus, as well as postganglionic sympathetic fibers from the celiac plexus. The submucosa of the small intestine contains the nerve plexus of Meissner. Between the longitudinal and circular muscle of the small bowel is the intramuscular myenteric (Auerbach's) plexus, consisting of nonmyelinated nerve fiber plus numerous ganglion cells.

The bowel wall is made up of an outer serosal coat, two layers of muscle (outer longitudinal smooth muscle and inner circular smooth muscle), a submucosal layer, and a mucous membrane composed of a single layer of columnar epithelial cells. Since the muscle and epithelial layers are relatively thin, the plane between these layers is difficult to establish surgically; therefore, tunneling procedures for ureters and catheterizable stomas may be quite difficult in the small bowel.

The physiology of the small and large intestine involves an intricate balance of water and electrolyte shifts. The major mechanisms of intestinal transport of water and electrolytes are illustrated in Figure 57.2. Water and electrolyte movement varies throughout the length of the bowel. These changes can be accounted for by both structural and functional differences between the small and large bowel. The major structural difference between the small and large bowel involves the "tight" junctions that join the epithelial cells (Figure 57.2). These tight junctions have characteristic permeabilities and ionic conductance that form the basis for paracellular ion and water movement.[28] Because such junctions are tightest in the colon and more permeable or leaky in the proximal small bowel, paracellular movement may account for a significant portion of water and electrolyte transport in the small bowel, and not play as important of a role in the colon.

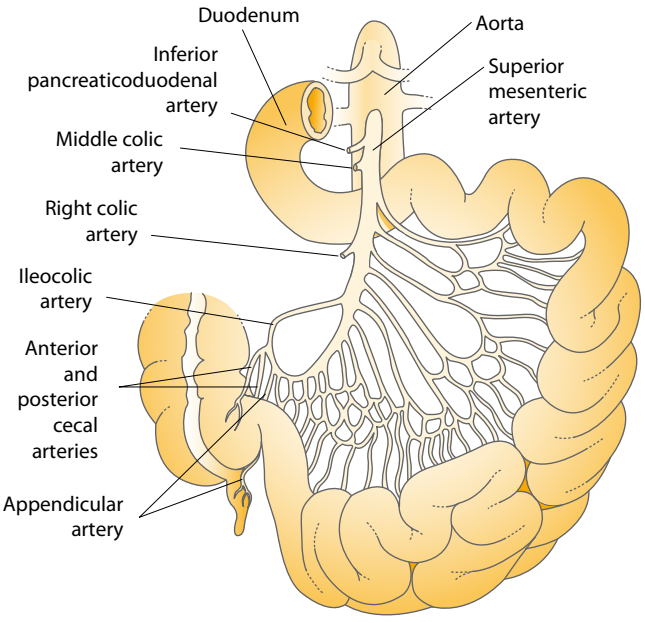

FIGURE 57.1 Arterial blood supply to the small intestine. The portion of the ileum with the longest mesentary that is commonly used for intestinocystoplasty is around 20–30 cm proximal to the ileocecal valve. (Adapted from Lindner H. *Clinical Anatomy*. Norwalk, CT: Appleton and Lange, 1989. With permission.)

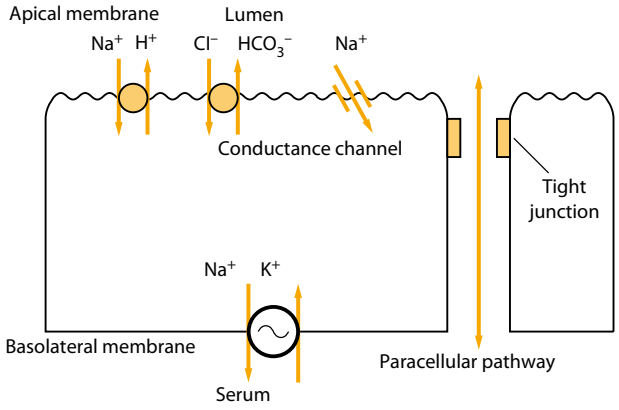

FIGURE 57.2 Intestinal transport mechanisms. Sodium absorption in both the small and large bowel is transcellular and occurs via a Na^+–H^+ exchanger on the apical membrane and a Na^+–K^+ pump on the basolateral membrane. The colon has an additional pathway of entry for Na^+ via conductance channels, which allows for noncoupled sodium absorption. Chloride and bicarbonate transport are coupled, which is pertinent in the development of metabolic acidosis following intestinocystoplasty. Water and electrolyte movement also occurs via paracellular pathways associated with tight junctions between the cells. Paracellular movement occurs more in the ileum than in the colon owing to leakier tight junctions. (Adapted from Lindner H. *Clinical Anatomy*. Norwalk, CT: Appleton and Lange, 1989. With permission.)

Although paracellular movement accounts for some of the bidirectional water and electrolyte transport, most of these shifts are thought to occur via transcellular mechanisms that occur through the intestinal absorptive cell. A characteristic example of the intestinal absorptive mechanism is the Na^+–K^+-ATPase enzyme, which is located on the basolateral membrane. This pump maintains low intracellular sodium concentrations, and thus creates an electrochemical gradient for sodium absorption, as well as passive transport of other electrolytes and water.

Sodium entry in the small bowel is accomplished by way of an Na^+–H^+ countertransport system in the apical membrane. In addition, a significant portion of the sodium entry into the colon also occurs via electrogenic Na^+ conductance channels that allow for noncoupled sodium absorption. The presence of this channel in the colon probably accounts for its ability to transport Na^+ and water against large gradients.

Chloride is absorbed throughout the entire small and large bowel. Bicarbonate is absorbed in large quantities in the jejunum but secreted in the ileum and colon. Chloride absorption in exchange for HCO_3^- secretion plays a large role in the transport of these electrolytes in the ileum and colon. Na^+–H^+ exchange and Cl^-–HCO_3^- exchange occur together. The net result is the electroneutral absorption of Na^+ and Cl^-.

Metabolic acidosis may develop whenever urine is in contact with ileal or colonic mucosa. The mechanism by which this hyperchloremic metabolic acidosis occurs is thought to be directly related to ammonium (NH_4^+) reabsorption that can occur along the entire small and large bowel. It is likely that the inhibitory effect of ammonium on Na^+–H^+ exchange allows ionized ammonium transport where it substitutes for sodium in the Na^+–H^+ exchanger.[29] The result of this ammonium absorption is increased Cl^- absorption in order to maintain electrical neutrality. This leads to hyperchloremia and eventual metabolic acidosis. Although the exact physiologic mechanisms of electrolyte transport continue to be defined, it must be remembered that the major function of the intestine, regarding this transport, does not change when intestine is used for urinary reconstruction. Continued fluid and electrolyte fluxes account for the majority of the physiologic problems associated with the use of intestine in the urinary tract.

Advantages and Disadvantages

Ileum is the most commonly used bowel segment for bladder augmentation. The advantages that are obtained with use of the ileum are (1) large quantity available, (2) ease in handling and reconfiguration, (3) predictable and abundant blood supply, (4) most compliant segment of the bowel, (5) moderate mucus production compared with colon, (6) less severe metabolic complications than the colon or stomach, and (7) fewer gastrointestinal complications than the cecum.

The disadvantages in using ileum include (1) occasional short mesentery that cannot reach the pelvis, (2) possible development of diarrhea and vitamin B_{12} deficiency when the most distal ileum is used, (3) difficulty with creation of submucosal tunnels, and (4) metabolic acidosis, as well as (5) bowel obstruction, (6) stone formation, (7) mucus production, (8) urinary tract infections (UTIs), and (9) tumor formation, all of which are risks with large bowel segments as well. These complications will be discussed later in the chapter.

Large Bowel

Through the early 1980s, the cecum and sigmoid colon were more commonly used than the ileum for enterocystoplasty. However, because of the shorter mesenteries, increased mucus production, and difficulty with configuration associated with the large bowel, the ileum has come to be the preferred segment of bowel for enterocystoplasty for most surgeons. Nevertheless, detubularized large bowel is still used for simple bladder augmentation in select patients.

Anatomy and Physiology

Anatomically, the large bowel can be divided into five sections: (1) the cecum and vermiform appendix, (2) the ascending colon and the hepatic flexure, (3) the transverse colon and mesocolon, (4) the splenic flexure and descending colon, and (5) the sigmoid colon.

The colon is 1.4–1.7 m in length. Its diameter is greatest on the right side, and gradually decreases as it approaches the sigmoid colon. The diameter of the sigmoid colon is often no wider than a loop of terminal ileum. The large bowel is made up of five distinct layers: serosa, muscularis externa, submucosa, muscularis mucosa, and mucosa. The outer serosal coat is a component of the peritoneum and normally completely covers the cecum, the appendix, and the transverse and sigmoid colon segments. The muscularis externa of the large bowel is composed of a complete inner circular and incomplete outer longitudinal layer of smooth muscle. The submucosa is composed of areolar tissue and lies between the muscularis externa and the muscularis mucosa. This layer contains the blood and lymphatic vessels supplying the bowel and is also the most important layer when developing an anastomosic site. The thin muscularis mucosa is made up of circular and longitudinal smooth muscle. The mucosa is composed of a layer of simple columnar epithelium containing goblet cells and is smooth and devoid of villi.

The muscle layers of the colon are notably different from those of the stomach, small intestine, and rectum. Longitudinal smooth muscle covers the large bowel incompletely. The longitudinal fibers are arranged in three narrow but distinct bands called teniae coli. The teniae of the cecum and ascending colon have a constant position relative to the bowel circumference. One band lies on the ventral surface of the colon, while the other two lie medial and lateral to the ventral band. The teniae of the transverse colon are less constant in position. Near the rectosigmoid junction, the teniae become quite indistinct. The unique anatomy of the teniae facilitates reimplantation of the ureters, appendix, and catheterizable stomas to create a reliable flap valve continence mechanism. The deep circular muscular coat of the colon wall is visible between the longitudinal muscle fibers of the teniae. Contractions of the colon produce a pouching or saculations of the bowel between the teniae. These pouchings, or

haustra, are randomly distributed and are easily noted on gross examination and visible on x-ray studies.

Cecum and Vermiform Appendix

The cecum measures approximately 6 cm in length and lies caudal to the entrance of the ileum into the colon. It is the thinnest portion of the colon. The cecum is normally mobile. In more than 90% of individuals, it is completely covered with peritoneum and possesses no mesentery. In some patients, such as children with spina bifida and ventroperitoneal shunts, the cecum can become fused with the posterior abdominal wall. This in turn causes foreshortening of the peritoneal attachments, resulting in the cecum becoming more superiorly located in the right colic gutter.[30]

The terminal 14 cm of ileum, the cecum, the appendix, and the ascending colon are supplied by the ileocolic artery, which is the terminal segment of the superior mesenteric artery. The ileocolic artery ends just proximal to the ileocecal junction and then divides into four major branches. The most superior branch, the colic artery, passes to the ascending colon, anastomosing with the descending branches of the right colic artery initiating the right colic portion of the marginal artery of Drummond or mesenteric arcade (Figure 57.3).

The three bands of teniae coli originate at the base of the appendix. The appendix varies in length from 2 to 20 cm, with an average of 9 cm. In the majority of patients, the appendix is held in position by the posterior inferior ileocecal fold. In about 5% of patients, the mesentery of the appendix runs directly from the posterior peritoneum in the region of the ileocecal junction onto the midportion of the appendix, at which point it is usually joined by the appendicular artery, a branch of the ileocolic artery. The appendicular artery arises either as a branch of the posterior cecal artery or directly from the main ileocolic trunk. It may also arise from the ileal branch of the ileocolic artery. Regardless of its site of origin, the appendicular artery will usually pass dorsal to the most distal segment of the terminal ileum before it enters the mesoappendix.

Ascending Colon and Transverse Colon

The ascending colon occupies most of the right side of the abdominal cavity and extends from the cecum to the hepatic flexure. The blood supply to the ascending colon comes from the colic branches of the ileocolic artery, the right colic artery, and the right branches of the middle colic artery. The right colic artery is the most variable vessel in the colon and is absent in 5%–7% of people. The transverse colon receives blood from the left colic artery; however, the major supplier is the middle colic artery, which is a more direct branch of the superior mesenteric artery.

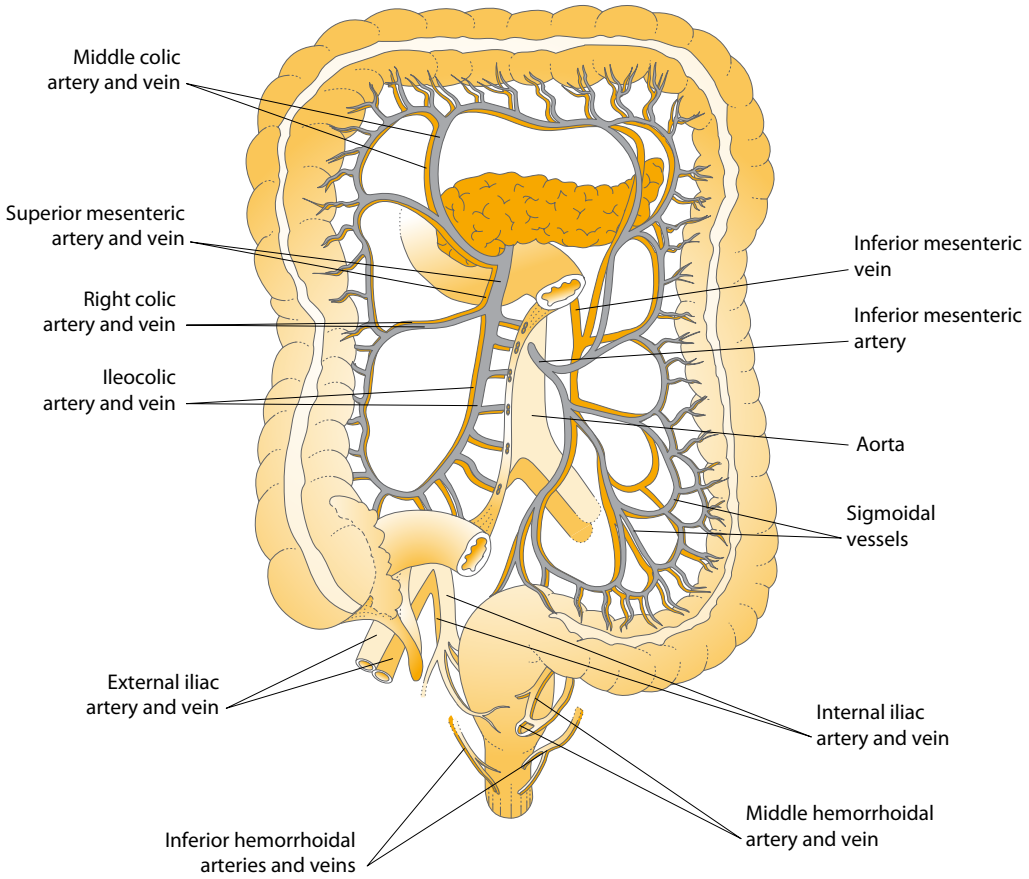

FIGURE 57.3 Arterial blood supply to the large bowel. Preservation of the marginal artery is extremely important when isolating portions of the colon for intestinocystoplasty. (Adapted from Lindner H. *Clinical Anatomy.* Norwalk, CT: Appleton and Lange, 1989. With permission.)

Sigmoid Colon

The sigmoid colon frequently has an S shape, and is divided into a fixed superior and a mobile inferior portion. The fixed portion of the sigmoid colon begins at the level of the iliac crest. The mobile portion of the sigmoid colon begins at the medial border of the left psoas major muscle and ends where it joins the rectum. The length, location of loops, degree of redundancy, relationship to other structures, and mobility of the sigmoid colon are markedly variable. It is very common in the spina bifida population to encounter sigmoid colon so enlarged and redundant that the mobile portion crosses the midline and lies anterior to the cecum.

The inferior mesenteric artery is the major vessel to the left transverse colon, the splenic flexure, the left colon, the sigmoid colon, and the rectum. The left colic artery is the first branch of the inferior mesenteric artery and runs in the direction of the superior half of the descending colon. The ascending branch of the left colic artery runs superiorly and parallel with the left colon, contributing to the marginal artery of Drummond. The descending branch of the left colic artery supplies the fixed segment of the sigmoid. The sigmoid arteries, which are second branches of the inferior mesenteric, supply the lower portion of the descending colon, the sigmoid colon, and a small segment of the upper rectum.

Advantages and Disadvantages

The ileocecal segment and cecum have been used extensively in reconstructive urology. One major advantage of these segments is utilization of the portion of bowel that has the largest diameter, resulting in a capacious and compliant reservoir that often fits the bladder base neatly. It has a well-defined blood supply that is reliable. The modified ileocecal valve can also be used as an antireflux or continence mechanism.

The major disadvantage in using the ileocecal segment is related to the loss of the ileocecal valve in the intestine. Patients with neurologic disorders or short gut may have an increased incidence of diarrhea and difficulty with fecal continence following removal of this segment from the intestinal tract. In addition, it is not available in the cloacal exstrophy population, who have little or no hindgut. The ileocecal segment also reabsorbs urinary wastes, which may result in hyperchloremic acidosis. Finally, cecum usually produces more mucus than the ileum, which can lead to increased infections and stone formation.

The major advantage in using sigmoid colon is the redundancy that is present, especially in the spina bifida population. The mobile portion of the sigmoid is so redundant in such children that it often lies in the right lower quadrant. It can be easily opened and reconfigured into a U shape to increase compliance. The thicker muscle can be used to create an antireflux ureteral anastomosis, as well as for placement of a tunneled continent catheterizable stoma, such as the appendix.

The major disadvantage in using the sigmoid colon is the reduced ability to create a large-capacity, compliant reservoir. The diameter of the sigmoid may be only as large as the ileum. In this circumstance, a segment of colon at least 20–28 cm is required to create an adequately sized reservoir. This amount of sigmoid colon can occasionally be difficult to obtain in the non–spina bifida population. Mucus production from the sigmoid is increased compared with the small bowel. This may increase the potential for the development of UTI and bladder stones. In the Indiana series, the highest spontaneous perforation rate occurred among those with sigmoid cystoplasties.[31] However, this has not been observed in other large series. Finally, hyperchloremic acidosis is more common when the sigmoid colon is used, compared with other bowel segments. Frequently, patients will need lifelong alkalizing agents, but this is also true after cecocystoplasty or ileocystoplasty.[32]

Surgical Technique

The goals of bladder augmentation are to provide a large-capacity, low-pressure urinary reservoir. Hinman[33] and Koff,[34] in particular, have documented the importance of detubularization and reconfiguration of the small and large bowel to facilitate maximum gains in capacity and compliance. Detubularization of bowel segments prevents synchronous contractions of the circular muscle of the gut. Since the radius of the reservoir is directly related to the volume, a greater radius in the augmented bladder translates into a larger low-pressure reservoir. The diameter of the reconfigured bowel segment increases with the number of folds that are incorporated during the reconfiguration (Figure 57.4). Regardless of the bowel segment used

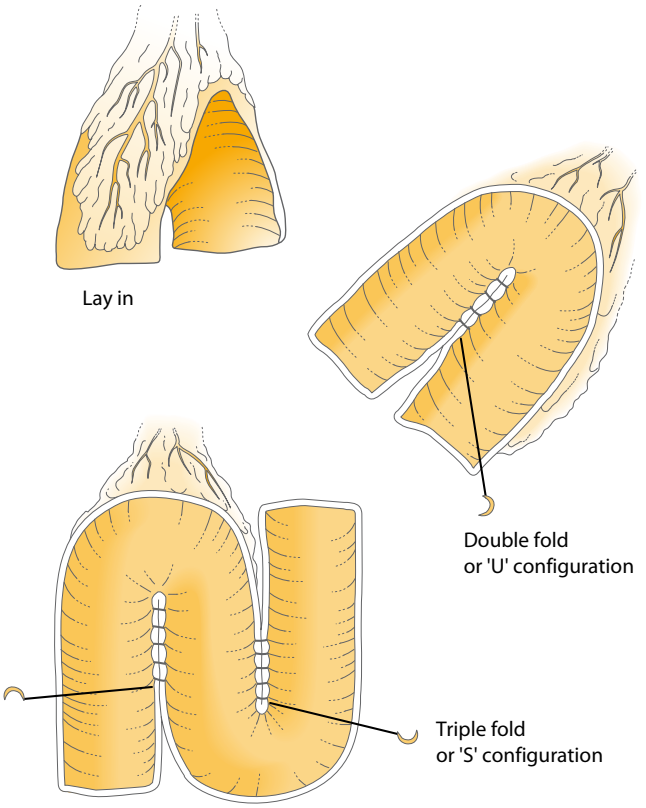

FIGURE 57.4 The detubularized ileum can be reconfigured in numerous ways. Each additional fold increases the potential radius of the augmented bladder. (Adapted from Rink RC, Adams MC. Augmentation cystoplasty. In Walsh PC et al., eds., *Campbell's Urology*, 7th edn., Philadelphia: WB Saunders, 1998, 3167–89. With permission.)

for augmentation, detubularization and reconfiguration should always be employed for both minimally invasive and open techniques, described below.

Ileocystoplasty

Enterocystoplasty is very reliable in lowering storage pressures and expanding the capacity of the noncompliant bladder. Ureteral implantations and procedures to increase outlet resistance can safely be undertaken at the same time. However, not every augmentation is completely successful. This may be related to the bladder having a great tendency to re-form itself, turning the augmentation into a diverticulum with a relatively small opening. To prevent this, the bladder should be bivalved ("clamshelled") from the bladder neck ventrally to the trigone posteriorly. Alternatively, when the bladder is small and thick walled, the "star" modification can be performed (Figure 57.5).[35] The star procedure involves opening the bladder in the sagittal plane. A second incision is then made in the coronal plane. If ureteral reimplantation or bladder neck reconstruction is being performed, the second incision is not made until after these procedures are completed. The authors will also occasionally employ an upside-down U-shaped or Boari flap modification for the initial bladder opening when a catheterizable stoma is being positioned at the umbilicus. In severely diseased bladders from tuberculosis, schistosomiasis, interstitial cystitis, and rarely bladder exstrophy, supratrigonal bladder excision is sometimes necessary, as in neuropathic bladders, when the walls are very thick. Whatever type of bladder opening is used, the goal is the same: to provide a wide bladder plate to which the bowel segment can be sewn, thus preventing a narrow anastomosis or hour-glass deformity that might result in the augmentation becoming a diverticulum.

When using ileum for enterocystoplasty, the segment chosen should be at least 15 cm proximal to the ileocecal valve to prevent vitamin B_{12} malabsorption, diarrhea due to malabsorption of bile salts, and potential injury to the blood supply to the cecum. Guidelines on the length of the ileum required to obtain the appropriate size and shape of the augmentation vary.[34,36] Most commonly, an ileal segment between 20 and 35 cm in length is used. However, a slightly longer segment may be required in an older child or an individual with a severely diseased and contracted bladder.

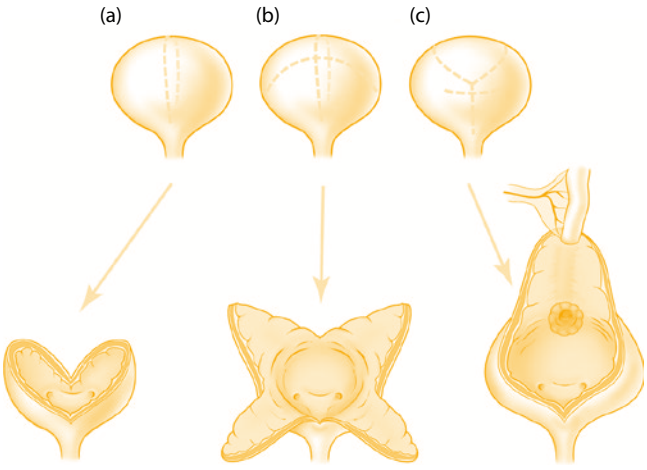

FIGURE 57.5 The native bladder can be opened in several ways: (a) bivalved in a clam-like fashion with full extension of the incision into the bladder neck to prevent an hourglass deformation of the augmented bladder, (b) the star modification, and (c) a U incision to create a flap of bladder that can be used for tunneling when creating a continent catheterizable stoma to the umbilicus.

Prior to harvesting the ileal segment, it is important to ensure that the mesentery reaches well down into the pelvis. Extensive mobilization of the mesentery is sometimes required if it is foreshortened. This is most common in the spina bifida population, often secondary to spinal abnormalities and the intraperitoneal adhesions that occur from the ventriculoperitoneal shunt. Once the appropriate bowel segment has been selected, the bowel is divided between straight clamps. The authors prefer to perform a single-layer hand-sewn ileoileostomy. A two-layer hand-sewn or stapled anastomosis can also be used. Closure of the mesenteric window with interrupted permanent sutures then completes the anastomosis. The isolated ileal segment is detubularized along its antimesenteric border after thorough intraluminal irrigation with normal saline. The ileal segment is then reconfigured into a U, S, or W (Figure 57.6).

After opening the native bladder as described above, the reconfigured bowel segment is anastomosed to the bladder with a full-thickness absorbable suture beginning at the posterior apex of the opened native bladder. Once the posterior aspect of the running, locking anastomosis has been completed, a second running, locking suture beginning at the bladder neck apex is begun and carried along the lateral aspect to meet the previous suture. Before final closure of the anastomosis, a suprapubic tube is brought out through the native bladder wall. After completion of the augmentation, the bladder is inflated and a watertight anastomosis confirmed by irrigation. A Penrose or closed suction drain is usually left in place along the posterior and anterior aspects of the bladder. The bowel is then examined to confirm its integrity, and the abdomen is closed in an anatomic fashion using heavy, running, absorbable sutures.

Ileocecocystoplasty and Cecocystoplasty

The ileocecal segment and cecum have frequently been used for augmentation cystoplasty. The cecum alone is rarely used. Simple detubularization and reconfiguration can be performed. The terminal ileum can be detubularized and incorporated into the cecal segment to increase total volume (Figure 57.7). Continuity of the bowel is reestablished with an end-to-side ileocolostomy. The reconfigured ileocecal segment is then anastomosed to the bivalved bladder with a single or double layer of running, locking, absorbable suture. Alternatively, the terminal ileum can be used for ureteral replacement when the ureters are short or the ileum can be tapered and used as a continent catheterizable stoma.

Sigmoid Cystoplasty

The sigmoid colon easily reaches the bladder and can be used for augmentation cystoplasty. It is especially valuable when reimplantation of ureters or a catheterizable stoma

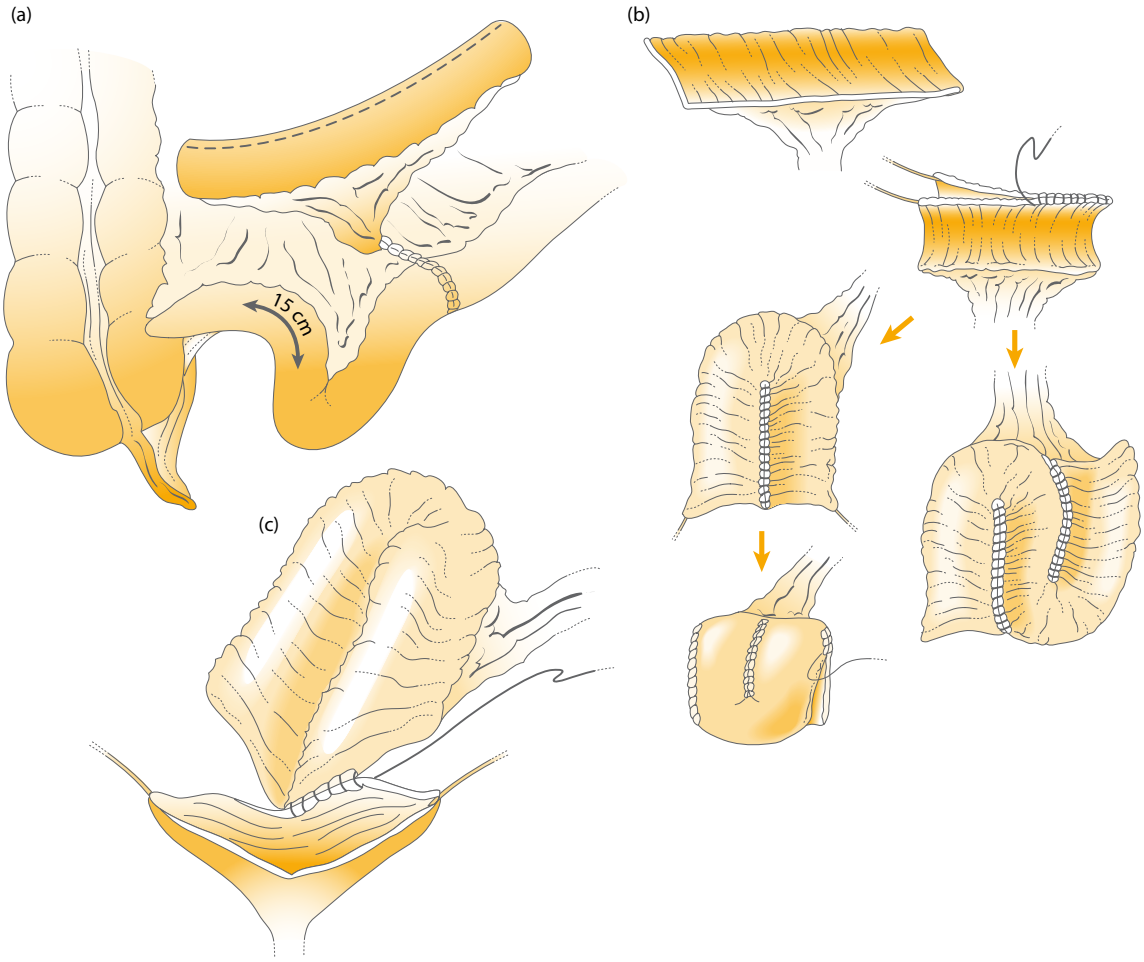

FIGURE 57.6 Ileocystoplasty. (a) A dependent portion of the ileum that is 20–30 cm long and a minimum of 15 cm proximal to the ileocecal valve is isolated and detubularized. Bowel continuity is reestablished with an end-to-end ileoileostomy. (b) Depending on the size of the ileal segment, it can be reconfigured and folded in several ways, including the U, S, and W (not illustrated) configurations. In addition, the edges of the reconfigured bowel can be sewn together to create a cup patch. (c) The anastomosis of the reconfigured bowel to the native bladder begins in the posterior apex of the opened bladder. (Adapted from Rink RC, Adams MC. Augmentation cystoplasty. In Walsh PC et al., eds., *Campbell's Urology*, 7th edn., Philadelphia: WB Saunders, 1998, 3167–89. With permission.)

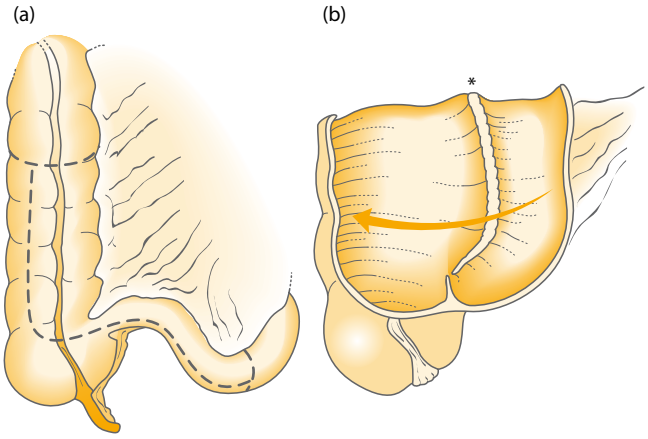

FIGURE 57.7 Ileocecocystoplasty: The ileum and cecum are isolated as a single unit (a) and reconfigured to form a "cup" for augmentation (b). * = suture line between the ileum and cecum. (Adapted from Rink RC, Adams MC. Augmentation cystoplasty. In Walsh PC et al., eds., *Campbell's Urology*, 7th edn., Philadelphia: WB Saunders, 1998, 3167–89. With permission.)

is not possible in the native bladder because the sigmoid musculature can easily be separated from the muscosa facilitating tunneling. Twenty centimeters of sigmoid is usually sufficient to achieve an adequate capacity after the segment is reconfigured. It is important to detubularize the sigmoid in order to prevent high-pressure coordinated contractions. Several techniques of sigmoid reconfiguration have been described (Figure 57.8). The authors prefer the U or S configuration because of simplicity and the possibility of significant contractile activity that may result from the method described by Mitchell[37] (Figure 57.8c). When the sigmoid segment has been isolated, colon continuity is reestablished with a single-layer, hand-sewn, end-to-end colocolostomy. The reconfigured sigmoid segment is then anastomosed to the native bladder in a similar fashion as described for ileum.

Postoperative Care

Following enterocystoplasty, parenteral antibiotics are continued for 48 hours unless the intraoperative urine culture is positive. Then, a full 7 days of culture-sensitive coverage

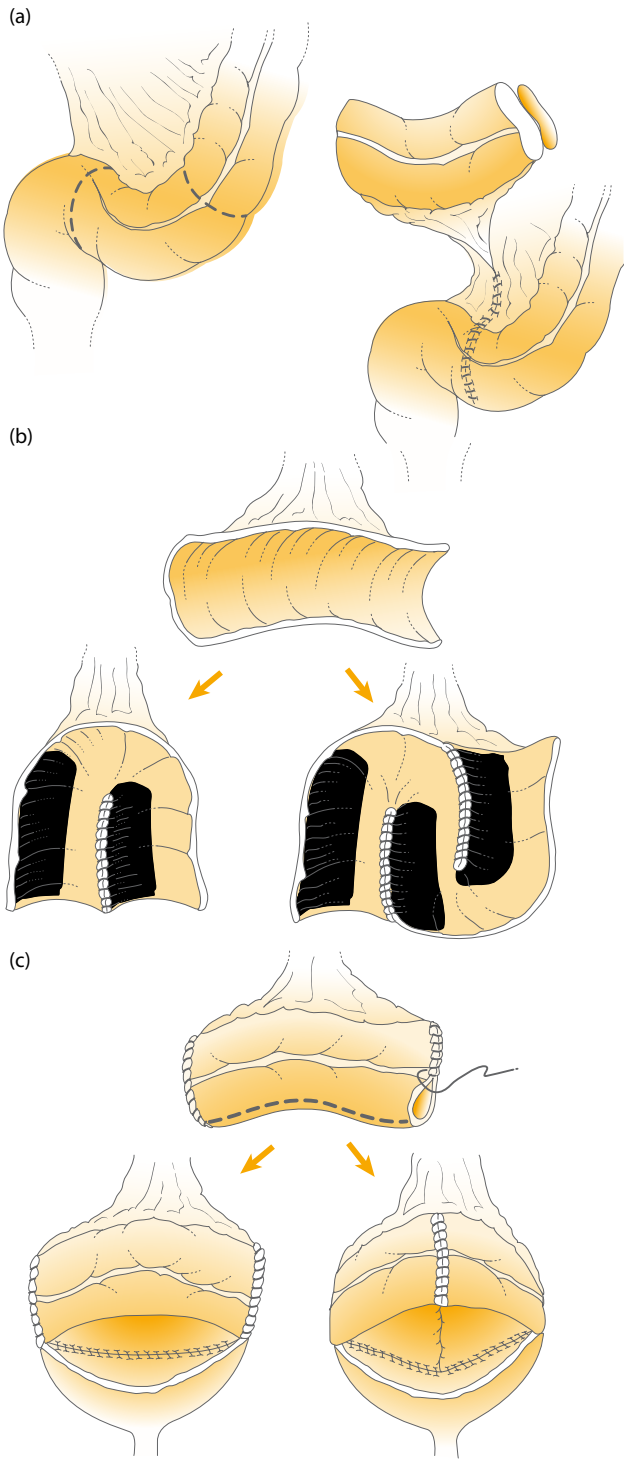

FIGURE 57.8 Sigmoid cystoplasty. (a) A portion of the sigmoid colon is isolated. (b) The sigmoid can then be reconfigured in a similar fashion as is performed for ileocystoplasty, with detubularization and folding back on itself. (c) Alternatively, the colonic segment can be closed at both ends, opened along the antimesenteric border, and then anastomosed to the bladder. This latter method is less optimal owing to the persistence of high intraluminal pressures following augmentation. (Adapted from Rink RC, Adams MC. Augmentation cystoplasty. In Walsh PC et al., eds., *Campbell's Urology*, 7th edn., Philadelphia: WB Saunders, 1998, 3167–89. With permission.)

is used. A nasogastric tube is left in place overnight and removed on the morning of postoperative day 1. Urinary drainage is maintained through the suprapubic tube and a secondary catheter through either the native urethra or the appendicovesicostomy (when performed). Diligent observation is needed during the immediate postoperative period to ensure that obstruction of the catheters does not occur secondary to blood clots or mucus. Daily bladder irrigations are important to decrease mucus buildup in the bladder, which can lead to infection, stone formation, and inefficient emptying. Bladder irrigations can begin immediately after surgery with 30 mL three times a day. This is increased to 60 mL twice a day after discharge. Both the suprapubic tube and secondary catheter are left to gravity drainage for 2–3 weeks. The suprapubic tube is then plugged and the patient begins intermittent catheterization. Before this, a cystogram can be performed to ensure adequate healing and the absence of extravasation; however, it is not absolutely necessary. Adequate emptying of the bladder with catheterization can be confirmed by checking residual urine via the indwelling suprapubic tube. Once the patient demonstrates proficiency at performing intermittent catheterization, the suprapubic tube is removed. Daily irrigations to clear the bladder of mucus are then recommended. Patients are told to catheterize every 2–3 hours during the daytime and once at night for the next few weeks. The time interval between catheterizations is gradually lengthened depending on the compliance of the augmented bladder and the gradually increasing storage volumes. In general, adequate stretching of the augmented bladder occurs within 6 months so that most patients need only catheterize approximately four to six times during the day to stay dry and maintain safe filling pressures. If a patient is going to attempt spontaneous voiding, one should wait until at least 3 months after surgery and then follow postvoid residuals to ensure adequate emptying. Radiographic imaging of the augmented bladder and the upper urinary tract is performed approximately 3 months postoperatively.

Results of Ileocystoplasty and Colocystoplasty

Bladder Capacity and Compliance

The most common preoperative urodynamic finding in the pediatric patient with a neuropathic bladder in need of bladder augmentation is a small-capacity, poorly compliant bladder with or without evidence of hyperreflexia and bladder instability. Both small and large bowel segments, when detubularized and reconfigured, have been found to provide adequately compliant tissue for enterocystoplasty that ameliorates or eliminates these adverse characteristics.[38] Flood et al.[39] reported on 22 augmentation cystoplasties performed over a period of 8 years. Mean age at surgery was 37 years, with a range of 2–82 years. The major indication for augmentation cystoplasty was reduced bladder compliance. A detubularized ileal augmentation was performed in 67% of the patients; 30% had a detubularized ileocecocystoplasty, and the remainder had detubularized sigmoid augmentation. Mean follow-up was 37 months. Bladder capacities increased from a preoperative

mean of 108 mL to 438 mL postoperatively. Excellent or improved results by all parameters were achieved in 95% of these patients.[39] Kilic et al.[40] reported on 30 children who underwent intestinocystoplasty. Sigmoid was used in 11 cases, ileum in 6, and ileocecum in 2. Postoperative evaluations revealed a mean postoperative capacity of 237 mL in the colonic group, 240 mL in the ileal group, and 250 mL in the ileocecal group. Mean compliance was 20.6 mL/cmH_2O in the colonic group, 21.6 mL/cmH_2O in the ileal group, and 25.5 mL/cmH_2O in the ileocecal group. They concluded that ileal, ileocecal, and colonic augmentations all provided high-volume reservoirs of similar compliance. Quek and Ginsberg reported long-term results on 26 patients with neurogenic voiding dysfunction who underwent enterocystoplasty. Mean follow-up in these patients was 8.0 years. Ninety-six percent of the patients had near or complete resolution of urinary incontinence. Mean total bladder capacity increased from 201 cc to 615 cc. They concluded that bladder augmentation provides durable clinical and urodynamic improvement for patients with neurogenic bladder dysfunction.[41]

It is apparent that all segments of intestine, when appropriately reconfigured, can adequately increase the capacity of the native bladder. However, enterocystoplasty does not guarantee that the bladder will be free of hyperreflexia. Robertson et al.[42] reported the persistence of hyperreflexia in 23% of patients after enterocystoplasty and documented regular phasic contractions in 77% of the augmented bladders despite bowel detubularization. It should be mentioned that in a majority of the patients in this series, an ileocecal segment was used. Recently, Pope et al.[43] reported on 19 of 323 patients who had undergone primary enterocystoplasty but required a secondary augmentation owing to the persistence of high pressures. Twelve of the 19 patients had colocystoplasties (14% of the total colocystoplasties), 4 had gastrocystoplasties (10% of the total gastrocystoplasties), and 2 had undergone ileocystoplasty. Cecum was used in one (1%). It is apparent in this large series that colocystoplasties are more likely to allow high storage pressures to persist. However, it must be noted that not all the colocystoplasties were completely detubularized but instead reconfigured after the ends were closed, with the colon opened along the antimesenteric border. Given this, it is difficult in this series to compare colon with ileum that was reconfigured into an S or W shape. Nevertheless, these studies emphasize the importance of careful functional and urodynamic follow-up in patients after enterocystoplasty, since some will require anticholinergics or secondary augmentation due to failure of the original procedure to improve bladder capacity and compliance adequately.

In summary, it appears that both small and large bowel, when detubularized, can be used for cystoplasty to provide a compliant and large-capacity reservoir. However, the large bowel may retain increased contractile activity despite detubularization.[31,38] It appears that detubularized ileum has less energetic phasic contractions than colon, and therefore has potentially less risk for persistent high storage pressures.[43] Given these advantages of ileum over colon, it is the authors' preference to use ileum whenever possible when performing simple enterocystoplasty.

Metabolic Issues

Electrolytes

The major function of intact small and large bowel is to absorb food, fluid, and electrolytes. When urine is stored in the bowel for prolonged periods, there is increased absorption of urinary solutes, which increases the risk of metabolic derangement. Koch and McDougal[44] hypothesized that ammonium reabsorption plays a key role in the development of hyperchloremic metabolic acidosis in patients following intestinocystoplasty. In support of this hypothesis, Stampfer and McDougal[29] demonstrated in a rat model that ammonium inhibits the sodium–hydrogen exchanger, resulting in ionized ammonium transport where it substitutes for sodium in the exchanger. This then leads to the increased absorption of chloride to maintain electrolyte neutrality, resulting in the development of hyperchloremic metabolic acidosis. In patients with normal renal function, serum electrolytes are usually unaffected by enterocystoplasty.[45–47] However, in patients with impaired renal function, metabolic acidosis can be profound. Careful preoperative evaluation and judicious use of bowel is recommended in patients with chronic renal insufficiency.[48] A gastric segment or cutaneous diversion may be safer. Owing to the electrolyte problems that can often develop in patients with significant renal insufficiency, the authors recommend gastrocystoplasty rather than conventional enterocystoplasty in this patient population.

Bone Growth

Impaired bone growth and demineralization are major concerns related to prolonged acidosis. Demineralization occurs secondary to the increased excretion of titratable acid (bony buffers). These concerns have received a large amount of attention in the last decade. Hochstetler et al.[49] demonstrated in a rat model that animals with ileocystoplasty, when given an acid challenge, developed bone demineralization and decreased bone growth that can be corrected with bicarbonate therapy. Current basic science literature demonstrated that enterocystoplasty in rats impairs neither skeletal growth nor bone quantity, but leads to significant loss of bone mass when combined with resection of the ileocecal segment.[50,51] This same group has also reported histomorphometrically that bone loss occurs after enterocystoplasty in the rat model.[50,51]

The more recent clinical literature has not clarified the true incidence or effect on bone growth. Mundy and Nurse[52] reported an average of 20% reduction in growth potential in three of six children who had colocystoplasties. However, no decrease in growth potential was noted in 10 children who had ileocystoplasties. They concluded that bone growth impairment was more likely after colocystoplasty than after ileocystoplasty. Two other reports demonstrated no impairment of bone growth or demineralization in children and adults after urinary reconstruction with various bowel segments.[47,53] However, two series have demonstrated variable degrees of reduction in bone mineral density in children with enterocystoplasties.[54,55] Finally, four other series have not demonstrated any effects of bone growth.[56–59] Interestingly, two of these reports are in bladder exstrophy patients; both of them

report growth retardation in this population with or without augmentation.[56,57] Further longitudinal studies will be required to clarify this issue. Therefore, until such studies are available, close observation for the development of acidosis and the treatment of any electrolyte abnormalities following intestinocystoplasty with bicarbonate therapy is recommended.

Bowel Dysfunction

Bowel dysfunction is known to occur occasionally after enterocystoplasty. Diarrhea can develop after resection of large segments of ileum, removal of the ileocecal valve, and extensive colonic resections. The incidence of bowel dysfunction following enterocystoplasty in all patients, including adults, has been reported to be between 10% and 54%.[15,60,61] In the spina bifida population, the incidence is approximately 20%. Since the overall incidence of bowel problems in children with spina bifida is further increased when the ileocecal valve is removed, one should try to avoid the use of ileocecal segments for augmentation in this patient population. Osmotic diarrhea has been theorized to occur after removal of the ileocecal valve, which results in a decreased transit time within the intestine.[62] It should be noted that these original data were not supported in a recent report by Husmann and Cain,[17] in which only 3% of their 63 ileal cecal cystoplasty patients had worsening of their bowel function. Despite this encouraging recent report, the authors feel that careful preoperative screening of patients with spina bifida with regard to their bowel habits is extremely important.

The diarrhea that develops postoperatively can be osmotic or secretory in nature. Secretory diarrhea is thought to occur because of decreased resorption of bile salts and subsequent fat malabsorption resulting in steatorrhea. Barrington et al.[63] reported on 14 patients who developed bowel difficulties after enterocystoplasty. They showed a direct correlation in many of these patients between their diarrhea and interruption of the enterohepatic circulation of bile acids. They also found that these patients can be identified by using bowel frequency charts and can be treated with anion-exchange resins.

Vitamin B_{12} Deficiency

Concerns regarding the development of vitamin B_{12} deficiency following small bowel resection or the use of small bowel for urinary reconstruction are well documented. The distal ileum is the major site of vitamin B_{12} absorption. It has previously been reported that up to 35% of patients will develop vitamin B_{12} deficiency following the construction of a Kock pouch, which uses about 80 cm of the small bowel.[64] Stein et al.[53] reported on 51 children who had undergone such reconstructions, but no significant drop in vitamin B_{12} levels was noted following surgery. From the older published data, it appears that the use of shorter segments of ileum, about 35 cm, as used for the Camey type 1 enterocystoplasty and conventional ileocystoplasty in children, did not place the patient at significant risk for vitamin B_{12} deficiency, even in the long term.[46] However, the Indiana group reported on more than 500 bladder augmentations and showed that there was a statistically significant correlation between follow-up time and serum B_{12}.[273] There conclusion was that pediatric patients who have undergone ileal enterocystoplasty are at risk for development of vitamin B_{12} deficiency. It was felt that the highest risk begins at 7 years postoperatively, and the risk increases with time. In a follow-up study, the same group demonstrated that oral vitamin B_{12} was effective in the treatment of vitamin B_{12} deficiency in patients with prior ileocystoplasty.[274]

It does appear that these patients are at some risk for vitamin B_{12} deficiency, and therefore the authors recommend harvesting small bowel segments that are at least 15 cm away from the ileocecal valve. The B_{12} receptor sites are clustered in the most terminal portion of the ileum, and this segment should be avoided. It is further recommended that vitamin B_{12} levels should be obtained yearly postoperatively. Oral administration of vitamin B_{12} is recommended when serum B_{12} levels reach the low normal levels (200–300 pg/dL). Alternatively, a vitamin B_{12} injection can be given prophylactically 3 years after enterocystoplasty. There is no evidence that the use of sigmoid colon for augmentation places patients at risk for vitamin B_{12} deficiency.

Mucus Production and Stone Formation

Mucus production and bladder stone formation are both complications related to the use of the gastrointestinal tract for urinary reconstruction. All segments of bowel produce mucus. However, mucus production from the ileum is less than that from the colon.[65] This has been confirmed clinically by several authors.[31,66] Mucus in the urinary tract is associated with an increased risk of infection.[67] Mucus production also increases during an acute infection, resulting in poor bladder emptying, especially when small catheters are used to drain the bladder.[36] Clinically, mucus production appears to decrease over time following ileocystoplasty. This is probably because of villus atrophy that occurs in the ileum. Colonic epithelium does not appear to undergo this type of change. Significant mucus production in colonic augmentations continues throughout the life of the patient.

The risk of stone formation after enterocystoplasty ranges between 7% and 52%.[68–73] The usual stone composition reported is magnesium ammonium phosphate (struvite), although several other stone compositions have been reported. Since the majority of stones are struvite in origin, it appears that chronic bacteriuria with urease-producing organisms may have a contributory role. However, it is also clear that the presence of mucus has an important role in the development of bladder stones following intestinocystoplasty. Mucus may serve as a biofilm that can harbor bacteria and promote further growth in a protected environment. Khoury et al.[74] have also demonstrated that the mucus from stone formers has increased levels of calcium, phosphate, and magnesium, and an increase in the calcium-to-phosphate ratio, compared with nonstone formers. This increased calcium-to-phosphate ratio may be clinically important in predicting which patients are at risk for stone formation. Given these findings, it appears that mucus has strong lithogenic properties and is a nidus for stone formation. Daily irrigation of the augmented bladder to prevent excess mucus buildup can be an effective measure to reduce the risk of stone formation in the

augmented bladder. Hensle et al.[75] recently reported that an irrigation protocol consisting of saline twice a week (240 mL) and gentamicin sulfate solution once a week (240–480 mg gentamicin/L saline, at 120–240 mL per irrigation, depending on patient age and reservoir size) significantly reduced the number of reservoir calculi from 43% to 7%. However, Brough et al.[69] did not observe a decreased incidence of stone formation when they instituted a regular bladder washout program in children following intestinocystoplasty.

Palmer et al.[73] identified an additional risk factor for the development of bladder stones in the augmented bladder. They noted the presence of hypocitraturia in some of their stone-forming patients. Treatment with oral potassium citrate returned urinary citrate levels to within normal values, and no recurrent calculi were then seen. Woodhouse and Robertson[272] have also reported that a metabolic screen in their augmented patients demonstrated that 80% of patients have risk factors for at least three different types of stones. All the patients were found to have an increase in urinary pH and hypocitraturia.

Bladder calculi in the augmented bladder are amenable to both open surgery and endoscopic management.[68,72,73,76,77] Neither procedure appears to have a clear advantage at this time. An open procedure is usually simpler when the stones are large, although new energy sources for the endoscopic treatment of stones, such as the holmium laser, may enhance the ability to manage bladder stones noninvasively. Miller and Park[78] have also described a method of using a laparoscopic entrapment sac percutaneously to control the loss of multiple fragments. This method has been used by the authors and has been highly successful. Treatment of bladder calculi needs to be individualized. Factors that should influence the surgical approach include the number and size of calculi, the previous bladder outlet procedure, the availability of endoscopic equipment, the availability of energy sources, and the surgeon's experience with endoscopic techniques.

Infections

Bacteriuria following enterocystoplasty is the rule since these patients are being intermittently catheterized. If the bladder is not emptied completely, symptomatic UTI may result. It is not known whether one type of bowel segment is at greater risk for the development of UTIs than another. Hirst[79] reported the presence of bacteriuria in 50% of sigmoid augmentations, whereas only 25% of ileocystoplasties had bacteriuria at any one time. In a series of 231 augmentation patients, Rink et al.[31] reported a symptomatic UTI rate of 22.7% following ileocystoplasty, 17.3% following sigmoid cystoplasty, 12% following cecocystoplasty, and 8% following gastrocystoplasty. They reported an overall 14% incidence of febrile UTIs with no statistical difference in the incidence between the various bowel segments. It appears that all augmented bladders are at risk for infection.

Tumors

Many fear that there may be an increased risk of malignancy in bladders after enterocystoplasty, as is the case after conventional ureterosigmoidostomy. Adenocarcinoma is the predominant tumor that develops after ureterosigmoidostomy, found most frequently at the site of the ureteral orifice. The latency period for tumor formation in the ureterosigmoidostomy patients ranges between 3 and 53 years, with a mean of 26 years. It is estimated that there is a 7000-fold increased risk of developing adenocarcinoma following ureterosigmoidostomy. It is with great trepidation that we enter the new millennium with hundreds of children having received enterocystoplasties without knowing whether there is an increased risk for the development of cancer. Filmer and Spencer[80] reported on 14 patients with tumor formation in the augmented bladder. Nine of these patients had ileocystoplasty, and colon was used in five. The exact etiology and pathogenesis of these tumors are unknown, but they seem analogous to those of cancers occurring after uterosigmoidostomy. Nurse and Mundy[81] studied 34 patients who had undergone augmentation cystoplasty or colonic substitution cystoplasty. A high incidence of histologic abnormalities in the intestinal segment was reported to occur along the anastomotic suture line and in the remaining bladder. Such abnormalities were directly correlated with heavy mixed bacterial growth in the urine and high levels of urinary N-nitrosamines. Woodhams et al.[82] have reported that there is no diurnal or long-term variations in urinary N-nitrosamine levels. They also found that levels were consistently higher in patients with inflamed or infected cystoplasties, those using intermittent self-catheterization, and those not taking antibiotic prophylaxis. Shokeir et al.[83] and Ali-El-Dein et al.[84] demonstrated that all bowel segments exposed to urine, regardless of their position (bladder or ureteral substitution), are at risk for malignant changes, and that urine cytologies may be a useful diagnostic tool in this setting. Barrington et al.[85] reported on four patients who developed tumors in augmented bladders. All the tumors were adenocarcinomas and were located on the bladder side of the anastomosis. It was concluded that these tumors were derived from the native urothelium. It was also demonstrated that transitional epithelium could undergo intestinal mucosal-like changes throughout the exposed native urothelium, including the renal pelvis, which was observed in one patient who had vesicoureteral reflux (VUR). Soergel et al.[86] reported 3 new cases of transitional cell carcinoma (TCC) from the Indiana augmentation database of 483 cases. Mean time from augmentation to TCC was 19 years. None of these patients had any additional risk factors. Thus, it is felt that development of bladder cancer is a real issue, and that all patients should undergo endoscopic surveillance beginning 10 years after initial surgery.

In 2009, Husmann performed an extensive review of the literature and found a total of 20 cases of bladder cancer following augmentation for congenital anomalies.[87] He reported that the incidence of cancer developing per decade following surgery was 1.5% for ileal and colonic and 2.8% for gastric bladder augmentations. Like all the reports of bladder cancer in this population, the majority presented with advanced and high-grade disease.

Austin et al. brought a new twist to the topic of risk of bladder malignancy in the spina bifida population when they reported eight additional spina bifida patients who developed bladder cancer between 1995 and 2005.[88] Mean age at presentation was 41, and only one patient

had previously undergone an enterocystoplasty. They combined their 8 patients with the previously reported 11 spina bifida patients, and only 7 of 19 had undergone bladder augmentation. This report demonstrated that all spina bifida patients, regardless of prior augmentation, appeared to be at increased risk for bladder cancer. In 2010, Higuchi et al. followed up on a similar theme of increased cancer risk for congenital bladder abnormalities.[89] Utilizing an extensive registry of patients with bladder abnormalities, they reported that there was no difference in the incidence of bladder cancer in patients with augmentation compared with a similar population without augmentation. They were able to demonstrate irrespective of augmentation status, patients on chronic immunosuppression for renal transplantation had a significantly higher incidence of bladder cancer. They concluded that bladder augmentation did not appear to increase the risk of bladder malignancy over the inherent cancer risk associated with the basic congenital bladder abnormality.

Previously, it was recommended that routine endoscopic surveillance for bladder tumors begin 7–10 years after augmentation.[86] However, this topic of surveillance became controversial based on three reports regarding the utility and cost–benefit of this type of program. Hamid et al. recommended it was not necessary to perform yearly cystoscopies in patients with augmented bladders, at least in the first 15 years, as cystoscopy had been unable to detect any cancers in this group.[90,275] They did recommend a complete workup, including cystoscopy and computed tomographic (CT) scan, of any patient that developed hematuria, suprapubic pain, or recurrent unexplained UTIs. In 2011, the Boston Children's Hospital group reported on the cost-effectiveness of screening spina bifida patients with cystoscopy and cytology.[91] They utilized a Markov model to compare two screening strategies. They concluded that annual screening for malignancy among the enterocystoplasty population was unlikely to be cost-effective at commonly accepted willingness-to-pay thresholds. Finally, Higuchi et al.[89] reported on the results of their screening program of 65 enterocystoplasty patients that were more than 10 years removed from their original enterocystoplasty. They concluded that annual surveillance endoscopy and cytology should be discontinued secondary to the low incidence of malignancy, lack of proven benefit, and enhanced cost containment.[90]

Enterocystoplasty is not the only group that appears to be at increased risk for bladder cancer. Two recent reports of metastatic transitional cell carcinoma arising after autoaugmentation have been published.[92,93] In both of these reports, the patients presented with gross hematuria 11 and 14 years, respectively, out from their initial autoaugmenation. Both patients eventually died of metastatic disease.

The issue of potential malignancy in augmented bladders and now the entire congenital bladder anomaly population cannot be overlooked or ignored. This is a potentially disastrous complication for children in whom one hopes to provide a surgically reconstructed bladder that will last for life. Future research is needed to determine the true risk of tumor formation, which children are at greatest risk, and whether premalignant changes can be detected endoscopically or with urine markers or cytology. Although the incidence of tumor formation following enterocystoplasty is unknown, lifelong urologic follow-up is required. Whether yearly cystoscopic evaluation and urine cytologies from the augmented bladder should be considered remains controversial. However, there is no controversy regarding the need for a prompt and complete workup for any congenital bladder patient that presents with a history of gross hematuria.

Perforation

Many complications can occur following enterocystoplasty. However, no complication is more potentially devastating or life threatening than unsuspected spontaneous bladder perforation. Although the exact incidence of perforation is not known, nearly every large series of enterocystoplasties includes at least one patient.[65,94–100] Among these reports, seven deaths have been directly attributed to such perforation.[101] Most of these deaths were due, at least in part, to delay in diagnosis. Therefore, a high index of suspicion is needed in any patient with a history of enterocystoplasty who presents with abdominal and/or shoulder pain.

It is not known whether one type of bowel is particularly prone to perforation after cystoplasty. Rink[37] reported a higher incidence of spontaneous perforations in sigmoid cystoplasties. He initially felt that the sigmoid colon was inherently at greater risk for perforation, but he now feel that this higher incidence may be more directly related to his initial technique of sigmoid detubularization. Others have reported that the highest incidence of perforation occurred when ileum was used.[95] DeFoor et al. believe that gastrocystoplasty may be at a lower risk for perforation.[102] However, it appears that no segment of bowel, tubularized or detubularized, is immune from this complication.

The etiology of bladder perforation is unknown. Initially, perforations were thought to be either linked to traumatic catheterization or a consequence of failure to catheterize on a timely basis.[96,99] However, perforation has been reported in patients who do not perform intermittent catheterization.[98] Another contributing factor in bladder perforation may be vascular compromise in the bowel wall. Crane et al.[103] reported that specimens from perforated bladders demonstrated histologic evidence of bowel wall ischemia. Also supporting the theory of bowel wall ischemia is an arterial perfusion study in a canine augmentation model, where a decrease in blood flow to the bowel wall was seen when the reservoir was overdistended and intravesical pressures were increased.[104] The perfusion change was most striking at the antimesenteric border in the detubularized bowel. In addition to overdistension, high pressures due to bladder hyperreflexia may lead to an increased risk of perforation. Bauer et al.[95] noted the presence of postoperative hyperreflexia in 40% of their patients who suffered a spontaneous perforation.

Some authors have suggested that a low urethral resistance is protective against both the high pressures associated with bladder hyperreflexia and failure to empty the reservoir on a timely basis.[94] However, Jayanthi et al.[105] reported on 28 patients who underwent complete bladder neck ligation in conjunction with enterocystoplasty with a catheterizable stoma. In this series, the one bladder

perforation that occurred was associated with blunt trauma and was not spontaneous in origin. Therefore, achieving total urinary continence surgically without a pop-off valve mechanism does not in itself increase the risk for spontaneous rupture.

There does not appear to be one single etiology or risk factor that makes some more prone to bladder perforation than others. Multiple factors are probably involved. Repetitive overdistension secondary to poor compliance, bladder hyperreflexia, and chronic infection all appear to place the augmented bladder at increased risk for spontaneous perforation.

The diagnosis of bladder perforation can be difficult at times, and a high index of suspicion is required to make the diagnosis quickly. Most pediatric patients who undergo enterocystoplasty are neurologically impaired. Lower abdominal sensation is diminished. Therefore, the clinical presentation may be nonspecific. Nausea, vomiting, fever, oliguria, and possibly referred pain to the shoulder secondary to diaphragmatic irritation may be presenting complaints.[106]

On physical examination, the abdomen is distended, with pain and irritation above the level of anesthesia. It may be difficult to distinguish pyelonephritis from a spontaneous bladder perforation. Thus, a standard or CT cystogram is recommended in any patient with an augmented bladder who presents with the above symptoms. Although the diagnostic role of a cystogram has been questioned in the past,[99,100] it is the most specific diagnostic radiographic test.[95,98] Braverman and Lebowitz[107] have recommended fluoroscopy during the filling phase to make sure that the bladder is completely distended in order to diagnose the perforation accurately. Residual contrast in the abdomen after the bladder has been drained establishes the diagnosis. Alternatively, an abdominal CT scan can be diagnostic and is helpful in demonstrating the extent of the extravasation.

When spontaneous perforation of the augmented bladder is suspected clinically and/or confirmed radiographically, immediate treatment is required. Catheter drainage, fluid resuscitation, and broad-spectrum antibiotics should be started immediately. In a stable patient, nonoperative management with catheter drainage, antibiotics, and serial physical evaluations may be all that is needed.[108] This nonoperative approach should be used only in selected patients in whom a small rupture is suspected. In the majority of patients, immediate exploration and closure of the bladder leak is safer. Intra-abdominal lavage, and irrigation and placement of intra-abdominal drains should then be done. Finally, all patients with an augmented bladder must be educated on the potentially lethal complications associated with delay in diagnosis of a spontaneous perforation. They should be instructed to inform a treating physician that they have an augmented bladder, and are at some risk for bladder perforation.

Obesity

An association has been reported in the adult literature between obesity and surgical complications, with increased wound infections being documented most commonly.[109–111] In their review of 1853 patients undergoing resection for gastric carcinoma, Bickenbach et al. reported increased postoperative complications for patients with a body mass index (BMI) of more than 25. Although there was no difference in overall survival, the rate of wound infections (8.9% vs. 4.7%) and anastomotic leaks (11.8% vs. 5.4%) was twice as high in the obese patients.[112] In the orthopedic literature, higher rates of infection and reoperation and additionally less improvement from their baseline were found in obese patients (BMI of more than 30) after surgery for degenerative spondylolisthesis.[113] Patients with myelodysplasia are often prone to obesity due to their mostly nonambulatory status and decreased energy requirements.[114] Donovan et al. reviewed the complication rates of patients with myelodysplasia who underwent bladder augmentations with creation of catheterizable stomas, with a mean follow-up of 39 months. Patients were categorized based on BMI as normal weight (<85th percentile), overweight (85th–95th percentile), or obese (>95th percentile). Obesity was found in 33% of patients, with a significant association between the presence of complications and weight category. Patients who were normal weight or overweight experienced complications in 40%, while obese patients demonstrated complications in 75%. As one of their study limitations, the authors acknowledged the difficulty of measuring BMI in myelodysplasia patients due to variations in height with spinal and lower extremity malformations.[115] The problem of adequately measuring the energy needs and BMI levels in children with myelodysplasia is currently being investigated in a multidisciplinary study at the Children's Hospital in Oklahoma City.

Quality of Life

The decision to proceed with augmentation of the bladder and other associated reconstructive procedures in children with a neurogenic bladder can be a complicated one. When the decision is based purely on the finding of upper tract deterioration, the decision is relatively straightforward since there is a definitive need to perform surgery to preserve renal function. However, in contrast, when the decision is being made for continence reasons, it can be difficult since it is not entirely clear what effect the surgery will have on the overall quality of life of the patient. This is especially true in individuals with spina bifida, where other forms of disability may impact their life more than bladder and bowel incontinence issues. As reconstructive surgeons, we are pleased when a patient that is wet becomes dry after lower urinary tract surgery. However, the perception of how surgical correction of incontinence truly impacts the patient's life may not necessarily be the same for the patient, parents, or surgeon. In a retrospective analysis of 36 patients with spina bifida, MacNeily et al. examined whether lower urinary reconstruction improves health-related quality of life (HRQOL). They did not find that there was a significant increase in the HRQOL score in these patients after surgery compared with age-matched controls.[116] In a follow-up prospective trial from the same institution, 31 patients with spina bifida were evaluated before and after surgery. Once again, no significant improvement in HRQOL domains was noted postoperatively.[117] However,

patient's self-assessment of improvement in continence postoperatively did not correlate well with that of the investigators, which may explain the lack of improvement in HRQOL. Additional studies in HRQOL in this unique patient population highlight the differences that can occur in HRQOL scores between patient reports and those from their parents.[118] The authors' own experience, as well as that of others that perform lower urinary tract reconstructive surgery, suggests that there are definite improvements in overall quality of life following reconstructive surgery in appropriately chosen patients. This disparity in experience from different institutions may relate to the appropriateness of the survey tools utilized to assess HRQOL, patient selection, investigator bias, and the tools to assess continence. Nevertheless, it is important that families be counseled about these quality of life issues preoperatively. Future studies will hopefully better clarify the true impact that bladder reconstructive surgery plays in patients' lives and those of their families, as well as specific patient characteristics that can better predict a positive result.

SURGICAL ALTERNATIVES TO INTESTINOCYSTOPLASTY

As discussed above, bladder augmentation with small and large bowel segments may result in electrolyte abnormalities, UTIs, mucus production, stones, and tumor formation. Most long-term complications are attributable to the presence of intestinal mucosa in a urinary tract reservoir for urine storage. In an effort to avoid the unwanted effects of enterocystoplasty, several alternative surgical procedures have been developed. These include gastrocystoplasty, ureterocystoplasty, autoaugmentation, and seromuscular enterocystoplasty.

Gastrocystoplasty

Gastric tissue was first reported to be applied to the urinary tract in 1956, when Sinaiko[271] described the use of a stomach segment for urinary diversion. Leong and Ong[119,120] subsequently reported the successful use of stomach for augmentation of the bladder in both dogs and humans. More recently, Mitchell and colleagues have modified Leong's original techniques for gastrocystoplasty and popularized its use in pediatric patients.[121,122] Since then, experience from multiple institutions over the past two decades indicates that the use of the stomach is feasible and effective in augmenting the neuropathic bladder. However, widespread use of stomach tissue as an alternative to intestine has been limited by the findings that the hematuria–dysuria syndrome (HDS) can be problematic in many patients (especially those that are sensate), and that in the long term, gastrocystoplasty does not appear to result in a reservoir that is as capacious and compliant as that which is achieved with conventional intestinocystoplasty. Regardless, the use of stomach tissue can be very advantageous and appropriate in some patients. For example, in patients with renal insufficiency and metabolic acidosis, gastrocystoplasty helps to buffer the adverse effects of the acidosis due to its ability to secrete acid into the urine. Thus, in select patients, the use of stomach for augmentation is a viable and appropriate alternative to the use of intestine.

Anatomy and Physiology

Anatomically, the stomach can be divided into five parts: the lesser curvature, greater curvature, fundus, body, and antrum. The layers of the gastric wall include the outer serosal coat, a muscular coat, the submucosal layer, and the epithelium. The muscular coat consists of smooth muscle fibers oriented in a longitudinal, circular, and oblique fashion. The epithelium of the gastric mucosa consists of a single layer of tall columnar epithelial cells and smaller acid-secreting cells. Loose areolar tissue in the submucosa lies between the mucosal and muscular layers. This loosely arranged layer allows technically simple separation of the mucosa from underlying muscle, permitting implantation of ureters in an antireflux fashion and tunneling of continent catheterizable stomas.

The entire arterial supply of the stomach is based on branches of the celiac artery, including the gastric, splenic, and hepatic arteries (Figure 57.9). The right and left gastroepiploic arteries supply the greater curvature and are pertinent for use in gastrocystoplasty. The gastroepiploic arteries arise from the right gastric and splenic arteries, respectively. They usually do not anastomose directly but are connected through small arterial branches.

The main physiologic function of the stomach is to digest food mechanically and chemically. Given this, the muscle of the stomach functionally contracts in a manner that is different from the rest of the intestinal tract in that it acts to churn its contents, as opposed to moving the bolus of food along a peristaltic wave. This unique pattern of contractility may be the cause of the phasic contractions that are seen in the augmented bladder following gastrocystoplasty.

The stomach chemically digests food through the secretion of acid. The exact mechanisms responsible for the control of acid secretion from the stomach are still not completely understood. Current evidence suggests that parietal cells, which are mainly located in the body of the stomach, secrete acid in response to gastrin that is released from G cells located in the antral mucosa. G cells, in turn, are stimulated to release gastrin by direct contact of the mucosa with food, antral distension, and vagal stimulation. Acid secretion can also be stimulated by acetycholine and histamine. The latter is important in that acid secretion from gastric segments following gastrocystoplasty can be inhibited with H_2 receptor blockers.

In addition to the stomach's ability to secrete chloride, other metabolic properties of importance include its barrier function to ammonium and chloride reabsorption. The combination of hydrogen ion and chloride secretion predisposes patients to the development of hypochloremic, hypokalemic, and metabolic alkalosis following gastrocystoplasty. However, this secretion of acid is beneficial in patients who have chronic acidosis associated with renal insufficiency.

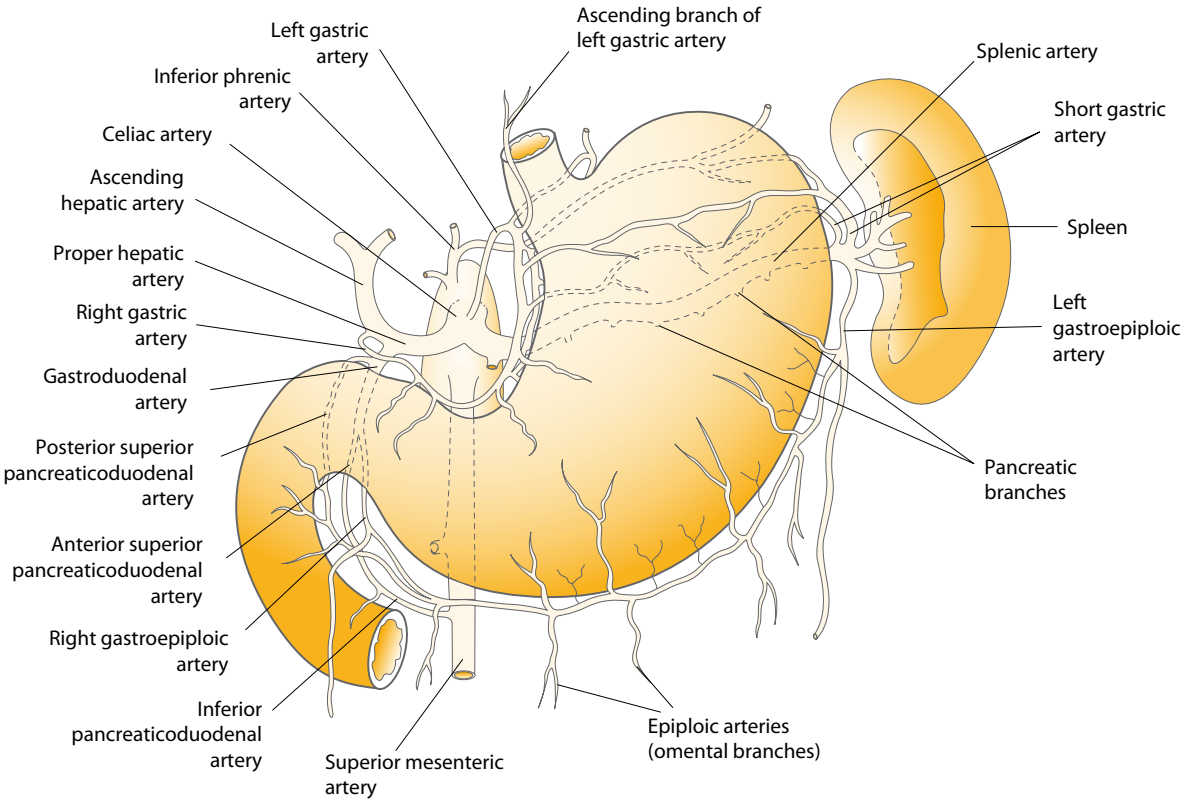

FIGURE 57.9 Arterial blood supply to the stomach. (Adapted from Lindner H. *Clinical Anatomy*, Norwalk, CT: Appleton and Lange, 1989. With permission.)

Advantages and Disadvantages

Surgically, the stomach is relatively thick and easy to work with. Use of the stomach for bladder augmentation has clear advantages in patients with renal insufficiency owing to its ability to secrete acid. This allows for buffering of systemic acidosis and reduces the need for bicarbonate supplementation. The resultant acid urine also appears to decrease the incidence of bacteriuria. In comparison with other intestinal segments, there is decreased mucus production and stone formation. The inherent musculature of the gastric segment may offer an additional advantage over small and large bowel by increasing the possibility for spontaneous voiding. This may result in more efficient emptying, less residual urine, and decreased need for intermittent catheterization.[123,124] Lastly, gastrocystoplasty can potentially be accomplished laparoscopically, which offers significant advantages in more rapid patient recovery following surgery.[125]

The main disadvantage of gastrocystoplasty that currently limits its widespread use in children with neuropathic bladders is the high incidence of HDS. This is most troublesome in patients who have a sensate urethra and perineum. Given this, caution should be exercised in selecting patients who are sensate and are at risk for incontinence (i.e., bladder exstrophy) when other enteric segments are available. This also applies when considering gastrocystoplasty in a patient with end-stage renal disease in need of transplantation, since ulcer formation and perforation of defunctionalized bladders have been reported.[126]

Postoperative studies suggest that gastrocystoplasty results in a less compliant and capacious reservoir than that usually achieved with conventional enterocystoplasty. Gastrocystoplasty may therefore be less useful in patients with a very small, noncompliant bladder plate.[40,127]

Surgical Technique

The original gastrocystoplasty, as described by Leong and Ong,[119,120] used the antrum of the stomach. Since incorporation of antral tissue may increase cyclical secretion of acid because of antral distension during bladder filling, more recent forms of gastrocystoplasty[121,128] favor utilization of a wedge taken from the greater curvature of the stomach that incorporates more body and less antrum (Figure 57.10). Depending on the individual vascular supply, this wedge of tissue may be based on either the right or left gastroepiploic artery. There is usually a vascular window between these arteries that defines which artery is dominant. Since the right gastroepiploic artery is longer and dominant in the majority of cases, this is more commonly used. A 10–15 cm length of stomach along the greater curvature is chosen, with special care taken to minimize inclusion of antral tissue. Branches of the gastroepiploic artery that are not directly supplying the wedge to be harvested are ligated. The wedge of stomach is isolated with the use of bowel clamps or an automatic stapler. The authors prefer the latter. The apex of the gastric wedge should be at least 1 cm below the lesser curvature to prevent injury to the vagus nerve and the right gastric

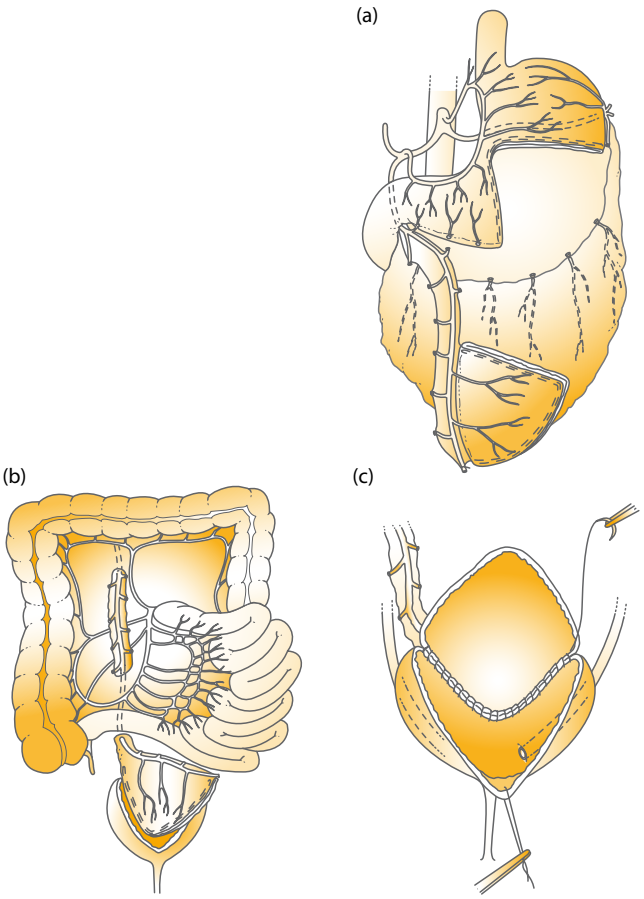

FIGURE 57.10 Gastrocystoplasty. (a) A wedge of stomach is isolated along the greater curvature of the stomach with its blood supply based on either the right or left gastroepiploic artery. (b) The flap is brought through the mesentaries of the small and large bowel or retroperitonealized following complete mobilization of the small and large bowel. (c) The flap is then anastomosed to the bivalved bladder.

vessels. Before isolation of the gastric wedge, it is advisable to ligate branches of the right gastric artery near the apex of the wedge, since failure to do this can result in significant blood loss.[129] A flap of greater omentum must also be mobilized along with the gastric wedge. The stomach is then closed in two layers. Alternatively, Raz et al.[130] have described a technique using an automatic stapler to harvest a gastric segment along the greater curvature of the stomach without opening the stomach.

Once the gastric segment is isolated, it is retroperitonealized by bringing it through the mesenteries of the transverse colon and small bowel. Special care should be taken to close these defects in the mesentery to prevent internal intestinal herniation. Alternatively, the right colon and duodenum can be mobilized up to the root of the small bowel mesentery, which allows placement of the gastric segment and its trailing vascular supply entirely in the retroperitoneal space. After the segment has been relocated inferiorly into the pelvis, it is rotated 90° to straighten the mesentery and vessels. The staples are then removed and the posterior tip of the stomach is sutured to the posterior aspect of the bivalved bladder using a running, interlocking 3-0 polyglactin suture.

Postoperatively, the augmented bladder should be adequately drained with a suprapubic tube and urethral catheter. A nasogastric suction tube is maintained for 3–5 days postoperatively. Following removal of the nasogastric tube and resumption of oral intake, the patient should be encouraged to eat small, frequent meals for the first few weeks to months.

Results

The urodynamic results of gastrocystoplasty are somewhat variable. Some authors report that it is useful in increasing capacity and compliance, similar to large and small bowel.[131] In studies that have analyzed both preoperative and postoperative urodynamics, gastrocystoplasty has been shown to increase bladder capacity by approximately 150%–200%.[132–134] However, it should be noted that there is a wide range of results reported with regard to increased bladder capacity following gastrocystoplasty.[40,128,131,133–135] In a recent series comparing the urodynamic findings and clinical outcomes following augmentation with stomach versus intestine, it was shown that both stomach and intestine are efficacious in improving compliance, but that the use of ileum and colon results in a higher-volume reservoir. Intestinal segments appear to expand more readily following augmentation than does the stomach.[40] Some of the differences in the literature regarding improvements in capacity and compliance following gastrocystoplasty may in part be explained by the variable amounts of stomach that have been harvested in individual patients. However, less volume expansion seems inherent to gastric segments when compared with the ileum and colon.

A unique postoperative urodynamic finding after gastrocystoplasty is the presence of low-amplitude, rhythmic contractions during bladder filling. These contractions are usually less than 30 cmH_2O.[121,135] However, contractions greater than 30 cmH_2O have been noted to be present in 10% of patients.[133–135]

Taken together, experience with gastrocystoplasty demonstrates that it is clearly an effective procedure in providing improvements in bladder compliance and capacity. However, in comparison with the ileum and colon, the stomach often results in a reservoir that is less capacious and perhaps less compliant.

HDS is unique to gastrocystoplasty. HDS is defined as the presence of pain in the bladder, suprapubic, or genital area; coffee-brown or bright-red hematuria in the absence of infection; skin irritation or excoriation; and painful urination or pain with catheterization. HDS occurs in up to one-third of patients and is the major factor that has limited the more widespread use of gastrocystoplasty in children requiring enterocystoplasty. In the largest series to date with long term follow-up, Plaire et al.[136] reported that 24% of patients following gastrocystoplasty had some element of this syndrome. Other retrospective series have reported the incidence of HDS to be as low as 2% and as high as 50%.[32,131,137] The disparity in these numbers likely relates to the variable makeup of the patient populations in each study. Also, longer-term follow-up may result in an increased incidence of complications.[138] In all studies evaluating HDS following gastrocystoplasty, a uniform finding is that HDS is much more prevalent in patients

who have a sensate urethra and perineum, whereas it is less common in patients who are insensate, as in patients with a neuropathic bladder secondary to spina bifida or spinal cord injury. Despite the relatively high incidence of HDS following gastrocystoplasty, most patients respond well to either H_2 receptor blockers or hydrogen ion pump blockers, such as omeprazole.[139] In some patients, alkaline irrigation of the bladder can also be used effectively.[140] A small percentage of patients may be refractory to all forms of conservative medical management, necessitating conversion to a different form of augmentation or diversion.[141]

The etiology of HDS is not entirely clear. Bogaert et al.[142] demonstrated that the gastric mucosa in the augmented bladder is stimulated in the same way as the native stomach. With this in mind, some authors have proposed that hypergastrinemia may be a causative or major contributing factor in patients with HDS. The association of hypergastrinemia and HDS has been demonstrated in several patients.[134,139,143–145] Despite this association, there has never been a direct correlation between this syndrome and aciduria and/or hypergastrinemia.[131,137]

Another potential complication associated with the use of stomach is peptic ulcer disease of the gastric patch with subsequent perforation.[126] It has been postulated that *Helicobacter pylori* infection may be an important etiologic factor in patients who develop ulcerative changes in the gastric portion of the augmented bladder.[146] Although patients are at significant risk for the development of HDS following gastrocystoplasty and other related complications associated with acid secretion by the stomach segment, it is rarely necessary to remove the gastric patch. Medical management of these problems is usually successful.

The beneficial effects of gastrocystoplasty in patients with reduced renal function and systemic acidosis are well documented.[121,123] However, the metabolic losses of acids and chloride may be overabundant, resulting in significant hypochloremic, hypokalemic, and metabolic alkalosis in some. This metabolic imbalance has been severe enough to warrant hospitalization in up to 7% of patients with gastrocystoplasty.[131,132] The precise mechanisms responsible for the development of a severe form of hypochloremic, hypokalemic alkalosis have not been precisely or sequentially elucidated. Significant risk factors appear to be recent viral illness associated with vomiting and other gastrointestinal losses, urinary concentrating defect,[121] renal insufficiency,[147] and the absence of acidosis prior to gastrocystoplasty.

As is the case with HDS, the development of hypergastrinemia following gastrocystoplasty has been postulated, although not definitively proven, to play a significant etiologic role in the development of metabolic alkalosis.[139,143,145] Clinical management of patients with hypochloremic, hypokalemic alkalosis includes aggressive intravenous rehydration with normal saline, replenishment of sodium and chloride, and use of H_2 receptor blockers. Once again, it is unusual to have an electrolyte abnormality that is so severe and unresponsive to medical therapy that removal of the gastric segment becomes necessary.

In comparison with conventional enterocystoplasty with small and large bowel, the incidence of bacteriuria and mucus production, and the development of bladder stones are significantly less following gastrocystoplasty.[71,121,135,148,149] The combination of decreased mucus, acidic urine, and the potential for spontaneous voiding (thus eliminating the need for intermittent catheterization) may be responsible for this decreased incidence.

Composite Gastrocystoplasty and Intestinocystoplasty (Gastrointestinal Composite)

As seen in the previous discussion regarding intestinocystoplasty and gastrocystoplasty, use of single enteric segments for augmentation has unique individual advantages and disadvantages. Since some of the metabolic effects of gastrocystoplasty are directly opposite of those with intestinocystoplasty, it has been proposed that some of these metabolic effects could buffer each other if both enteric segments are placed in combination. This concept was first introduced by Lockhart et al.[150] Ideally, the advantages of each segment could be retained and maximized with concomitant reduction of many of the undesired side effects. Namely, the stomach could still be retained for reimplantation of catheterizable tubes and ureters, while incorporation of a piece of ileum could reduce the side effects of increased acid secretion in the bladder (HDS) and enhance the urodynamic effects that are achieved with the use of stomach alone. Over the last decade, several reports have now demonstrated that gastrointestinal composite augmentation is feasible and advantageous in select patients.[151–154] The composite augment can be constructed either primarily or as a secondary procedure following a previous augmentation with a single piece of stomach or bowel. The size of each individual gastrointestinal segment can be varied depending on the individual metabolic and urodynamic needs of each patient. Austin et al.[153] have demonstrated that the beneficial reduction in acid load in patients with renal insufficiency can still be maintained with the gastrointestinal composite augmentation, while the buffering effects of the incorporated intestine help to reduce the incidence of HDS. In addition, the incidence of bacteriuria and stone formation is lower in composite reservoirs than in intestinocystoplasty alone, presumably in part due to the lessened mucus production from the gastric segment. Although technically demanding, gastrointestinal composite augmentation appears to be a viable and improved form of augmentation in select patients with short bowel syndrome, metabolic acidosis, and renal insufficiency.

Autoaugmentation

Autoaugmentation, also known as vesicomyotomy and vesicomyectomy, was introduced by Cartwright and Snow.[155,156] This is a novel approach to bladder augmentation that aims to enlarge bladder capacity and improve bladder compliance without using a patch graft or opening the bladder. In essence, this procedure creates a large bladder diverticulum by removal of the bladder muscle from the dome. The most important advantage for this procedure is the avoidance of intestinal epithelium with its associated complications. The native urothelium is preserved. The major drawback of autoaugmentation is that experience has failed to identify the most

appropriate patients for this procedure. Mixed results have been obtained clinically with regard to symptomatic and postoperative urodynamic improvement in the autoaugmented bladder. Evaluation of the available data indicates that there is no direct correlation between preoperative urodynamic findings and success. Therefore, it continues to be a procedure that can work well in some patients while it fails in others. Nevertheless, it appears that this procedure is best suited for patients with reduced compliance in combination with a near-normal preoperative bladder capacity.[157–159]

Despite the problems in predicting surgical success preoperatively, it seems reasonable to consider autoaugmentation as an option in some patients in whom conventional enterocystoplasty is needed and there is a desire to avoid the use of bowel. However, patients need to be aware of the relatively high failure rate of autoaugmentation in comparison with conventional eneterocystoplasty. Patients that should be excluded from consideration for autoaugmentation include those with failed bladder exstrophy repair, multiple previous bladder operations, and very small bladder capacities. Autoaugmentation in these children is more difficult technically, and results in general have been poor.[157,159]

Anatomy and Physiology

Autoaugmentation preserves the native bladder urothelium. The metabolic and physiologic properties of this urothelium following autoaugmentation are not well studied, although available data suggest that no significant changes occur. Following autoaugmentation, the mucosal herniation has been shown in both experimental animals and humans to have evidence of collagen deposition, neovascularity, variable inflammatory changes, and occasional muscle fibers.[159–161] No significant metaplastic or dysplastic changes in the native urothelium have been reported.

Advantages and Disadvantages

The primary advantage of autoaugmentation over conventional enterocystoplasty is preservation of the patient's native urothelium in the augmented segment. This avoids the complications associated with enterocystoplasty related to the presence of heterotopic epithelium in contact with the urine noted previously. However, this alone does not seem to eliminate the risk of bladder cancer.[92,93] Technically, autoaugmentation is an extraperitoneal procedure that can be performed through a Pfannestiel incision and avoids the complications of transperitoneal bowel surgery. Although autoaugmentation is usually performed without a formal cystotomy, other bladder procedures, such as ureteral reimplantation and appendicovesicostomy, can be carried out (intravesically or extravesically) at the same time. Lastly, it is important to note that autoaugmentation does not preclude further augmentation procedures if unsuccessful.

The main disadvantage of autoaugmentation is the inability to predict which patients will do well with this technique. An additional concern is the theoretical risk of bladder rupture that has been demonstrated in animal studies.[162,163] Although perforation of the autoaugmented bladder has been reported in only one patient to date,[164] the overall increased risk of bladder rupture compared with other types of bladder augmentation has yet to be defined.

Surgical Technique

Patients should receive a full bowel preparation preoperatively and be counseled on the possible need to perform an alternative type of augmentation if intraoperative findings dictate that autoaugmentation is not technically feasible. Specifics regarding the technique of autoaugmentation have been well described by Snow and Cartwright.[159] The procedure is usually performed through a Pfannenstiel incision and is done extraperitoneally. Once the bladder is mobilized, the peritoneal covering is entirely detached. Snow and Cartwright advocate the performance of intraoperative urodynamics, both before and after the autoaugmentation. Although not definitive, intraoperative urodynamics can be useful in making an assessment of potential success. It also assists in establishing the maximum volume following autoaugmentation to which the bladder can be safely distended during the immediate postoperative period.

Once initial intraoperative urodynamics is completed, the bladder is filled and a needle-tipped electrocautery is used to divide the detrusor musculature from the underlying epithelium (Figure 57.11). This is usually started ventrally in a vertical fashion. The plane between the underlying epithelium and the overlying muscle is then

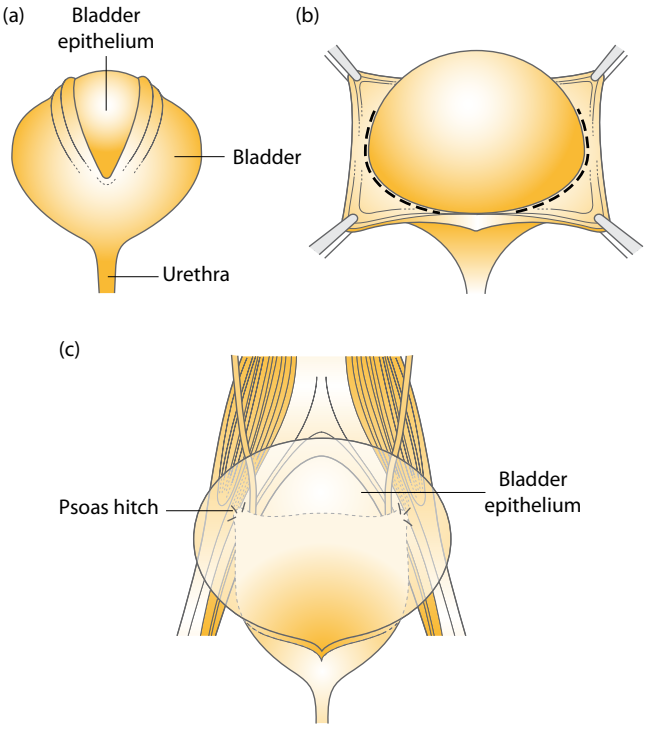

FIGURE 57.11 Autoaugmentation. (a) The detrusor muscle is incised in the midline and a plane is established between the muscle and the underlying mucosa. (b) This plane is further developed, and a large mouth diverticulum is created. (c) The remaining detrusor muscle is fixed posteriorly to prevent its coaptation. (Adapted from Cartwright PC, Snow BW. *J Urol* 1989;142:1050–3. With permission.)

identified and further developed using both blunt and sharp dissection. Special care is taken to avoid tears in the urothelium, since this can be difficult to repair in some cases and urinary extravasation postoperatively is associated with inflammation. Inability to distend the bladder postoperatively may result in contraction. When perforation does occur, it should be repaired with fine, absorbable suture. Removal of overlying muscle fibers continues until the detrusor musculature is removed from at least one-half of the bladder. Optimally, as much musculature is removed as possible. At this juncture, intraoperative urodynamics is repeated once again. If there is minimal to no improvement in bladder capacity and/or compliance, autoaugmentation should be abandoned and conventional enterocystoplasty undertaken following excision of the redundant bladder epithelium.

After autoaugmentation is completed, either one can excise the detached detrusor musculature or the remaining lateral bladder muscle can be attached to the psoas muscles. However, neither of these steps has been found to be essential for success.[159,165] Postoperatively, a urethral catheter and Penrose drain are left in place. Suprapubic tubes are avoided, as the bladder should be watertight. Experience has shown that bladder distension during initial healing is important for surgical success. This can be accomplished either by intermittent distension of the bladder to the capacity that was determined appropriate intraoperatively or by maintaining catheter drainage with constant bladder distension at an intravesical pressure of 20–40 cmH_2O. The catheter can generally be removed in 1–2 weeks. It is recommended that a cystogram be performed before catheter removal to exclude urinary extravasation.

Recently, several authors have demonstrated that technically successful bladder autoaugmentation can be accomplished laparoscopically.[166–169] Although a laparoscopic approach is feasible, further experience is necessary to determine whether this approach is clinically successful and cost-effective.

Results

The efficacy of autoaugmentation in improving bladder capacity and compliance has been varied. Cartwright and Snow[157] have reported follow-up of greater than 1 year in 30 patients, 19 of whom had a neuropathic bladder secondary to spina bifida. All patients had preoperative urodynamic evidence of reduced bladder compliance and detrusor hyperreflexia. While clinical success has been dramatic in some, the overall results have been less impressive. One-third of the patients had a significant increase in bladder capacity, an additional third were unchanged, while one-third had loss of capacity. Evaluation of bladder compliance revealed that 60% had an improvement in compliance by greater than 50% compared with preoperative measurements, 20% had a 20%–50% improvement, and the remainder did not change significantly. Following autoaugmentation, the majority of patients remained on intermittent catheterization, although 20% demonstrated the ability to void spontaneously. Seven of these 30 patients have required secondary enterocystoplasty.

Snow and Cartwright[159] have reevaluated preoperative parameters in these patients in an effort to identify specific factors that would help to prognosticate eventual outcome following autoaugmentation. Unfortunately, they were unable to identify any such factors. However, certain generalizations can be made from this analysis. Autoaugmentation appears to be poorly suited to patients with a history of bladder exstrophy or multiple prior bladder operations, since in these patients it is difficult to develop a plane between the bladder muscle and mucosa. Results have also been relatively poor in these groups. The ideal candidate is the patient with a near-normal bladder capacity but reduced compliance.

Since the original publications describing the autoaugmentation technique, several other centers have reported their experiences with autoaugmentation in children. Stothers et al.[170] performed autoaugmentations in 12 pediatric patients. They observed a mean increase in bladder capacity of 40% and a mean decrease in leak point pressure of 33%. Skobejko-Wlodarska et al.[171] have reported on the use of autoaugmentation in 21 children with spina bifida and found a modest increase in bladder capacity in two-thirds of patients and significant improvements in bladder compliance in another two-thirds. Two recent series with long-term follow-up in children with myelomeningocele have demonstrated less favorable results.[172,173] Both studies demonstrated that a majority of patients were considered surgical failures due to a lack of clinical and/or urodynamic improvement and a high incidence of patients requiring subsequent enterocystoplasty.

Finally, in a long-term functional outcomes assessment of autoaugmentation, Aslam and Agarwal reported on 33 patients with a mean follow-up of 148 months. A total of 10 of the 18 patients with idiopathic detrusor overactivity (55.5%) and 6 of the 15 patients with neurogenic detrusor overactivity (40%) showed marked improvement in symptoms. An overall success rate of 48.5% was achieved. The conclusion of this study was that autoaugmenation offers a reasonable long-term success rate to patients undergoing surgical treatment for refractory detrusor overactivity.[174]

The experience with autoaugmentation in the adult population appears to be more predictable and consistently favorable than the results described thus far in children. Stohrer et al.[175,176] reported on 50 adult patients from their spinal cord injury center. In patients with neuropathic hyperreflexive bladders that were refractory to medical therapy, bladder autoaugmentation was found to increase mean bladder capacity from 121 to 406 mL, with concomitant improvements in bladder compliance. Leng and colleagues[177] recently compared the efficacy of enterocystoplasty with autoaugmentation in adults. They reported on more than 60 patients undergoing either autoaugmentation or conventional enterocystoplasty. There were no significant differences in postoperative urodynamic parameters between enterocystoplasty and autoaugmentation in patients with refractory detrusor instability, interstitial cystitis, radiation cystitis, and other forms of neuropathic bladder. An important finding was that enterocystoplasty was uniformly superior to autoaugmentation in patients with a history of myelodysplasia. The overall improvement in the results of autoaugmentation in adults may be related

to differences in the bladder disease processes and patient population. Autoaugmentation is mostly performed in children with a neuropathic bladder from congenital causes, while in adults the neuropathic bladder is usually an acquired condition. It may be that autoaugmentation is more successful in adults because surgery is undertaken earlier in the disease process, prior to irreversible histologic and functional changes in the bladder wall.

Seromuscular Enterocystoplasty

Seromuscular enterocystoplasty involves the use of a demucosalized flap of the colon, stomach, or ileum. The removal of the gastrointestinal mucosa results in a denuded seromuscular flap that can be either (1) used alone as an augmentation flap that is subsequently reepithelialized with native urothelium from the native bladder, or (2) used in conjunction with autoaugmentation in which the seromuscular is placed over the exposed bladder mucosa of an autoaugmented bladder. The use of a demucosalized segment of bowel for bladder augmentation was first described by Shoemaker in 1955.[178,179] He was able to show that seromuscular bowel flaps, when placed into the bladder wall with the denuded side either inward or reversed, such that the serosa faced the lumen of the bladder, were reepithelialized by urothelium. Unfortunately, subsequent long-term studies in small and large animals have consistently demonstrated that seromuscular bowel segments alone scar and contract.[180–183] Histologic evaluation suggests that the scarring is due to the trauma associated with the demucosalization process and/or a prolonged inflammatory response in the denuded bowel before the reepithelialization of the seromuscular flap from the native bladder urothelium occurs.

The intention of seromuscular enterocystoplasty is to combine the advantages of conventional enterocystoplasty while preserving the native urothelium of the bladder. This procedure ideally results in a muscle-backed augmentation flap that is lined with urothelium. Contraction of the seromuscular flap is hopefully avoided by either rapid regrowth of native urothelium over the demucosalized surface or adherence of the native urothelium to the demucosalized gastrointestinal segment (when combined with autoaugmentation). Numerous animal studies have demonstrated that seromuscular enterocystoplasty with or without autoaugmentation can successfully augment the bladder with elimination of the complications related to retained intestinal epithelium.[184–188] However, clinical experience thus far has been mixed and varied. Early experience with this procedure suggested that the success may be limited by the same factors that give rise to inconsistent results with autoaugmentation. More recent modifications of the technique, including improved methods for demucosalization and constant distention of the seromuscular flap during the initial postoperative period, have demonstrated that more reliable results are possible. Further experience with long-term follow-up is needed to better determine the factors that are important in predicting success and whether this type of augmentation remains stable without future fibrosis, loss of compliance, and/or metaplastic changes. Nevertheless, seromuscular enterocystoplasty represents an intriguing advancement in bladder augmentation techniques whose appropriateness for routine use in children is currently being defined.

Anatomy and Physiology

Seromuscular enterocystoplasty has been accomplished with stomach, ileum, and colon. The metabolic consequences of seromuscular enterocystoplasty are presumed to be minimal, since the native urothelium is kept intact. This assumption is supported in part by animal studies.[187] Histology from these studies reveals that the urothelium covering the seromuscular flap appears normal.[188,189] Whether late metaplastic changes will occur in the bladder urothelium when it is placed in direct contact with a seromuscular segment of bowel is not known. It has been well documented that stromal–epithelial interactions in other individual organs are important for normal cell growth and function.[190,191] The stroma of the bowel segment may adversely affect the overlying growth and function of the bladder urothelium in the long term.

Advantages and Disadvantages

The advantages of this procedure are similar to those of autoaugmentation, with the most important being preservation of the native urothelium. This avoids the aforementioned complications associated with the interposition of heterotopic intestinal epithelium in the urinary tract. Since it has been shown that partial reepithelialization of the seromuscular segment with enteric epithelium can occur, it is not clear that these problems will totally be avoided. This is especially important when considering the long-term risk of tumor formation, since the presence of any intestinal mucosa is clearly worrisome. An advantage of seromuscular enterocystoplasty over autoaugmentation alone is the provision of adequate muscle backing of the augmented segment. This may potentially reduce the risk of scarring and fibrosis and may lessen the risk of spontaneous perforation.

There are currently two major disadvantages to this procedure. It is a technically demanding procedure and much more labor-intensive than conventional augmentation cystoplasty or autoaugmentation alone. In addition, clinical experience is limited, and the available published results are mixed with regard to postoperative urodynamic improvements. Postoperative distension of the augmented bladder appears to be an important factor for the success of this procedure. Thus, some authors have advocated routinely increasing bladder outlet resistance with seromuscular enterocystoplasty and the avoidance of concomitant intravesical procedures when possible.[158]

Surgical Technique

Seromuscular enterocystoplasty is initially begun by isolating a segment of the stomach, ileum, or colon (Figure 57.12). The isolated segment of the stomach or bowel is then detubularized. The most difficult and technically demanding portion of this procedure is demucosalization of the flap. The plane of dissection and whether the submucosa should remain with the seromuscular flap is a point of contention. It has been suggested by some authors that the muscularis mucosa (which is contained

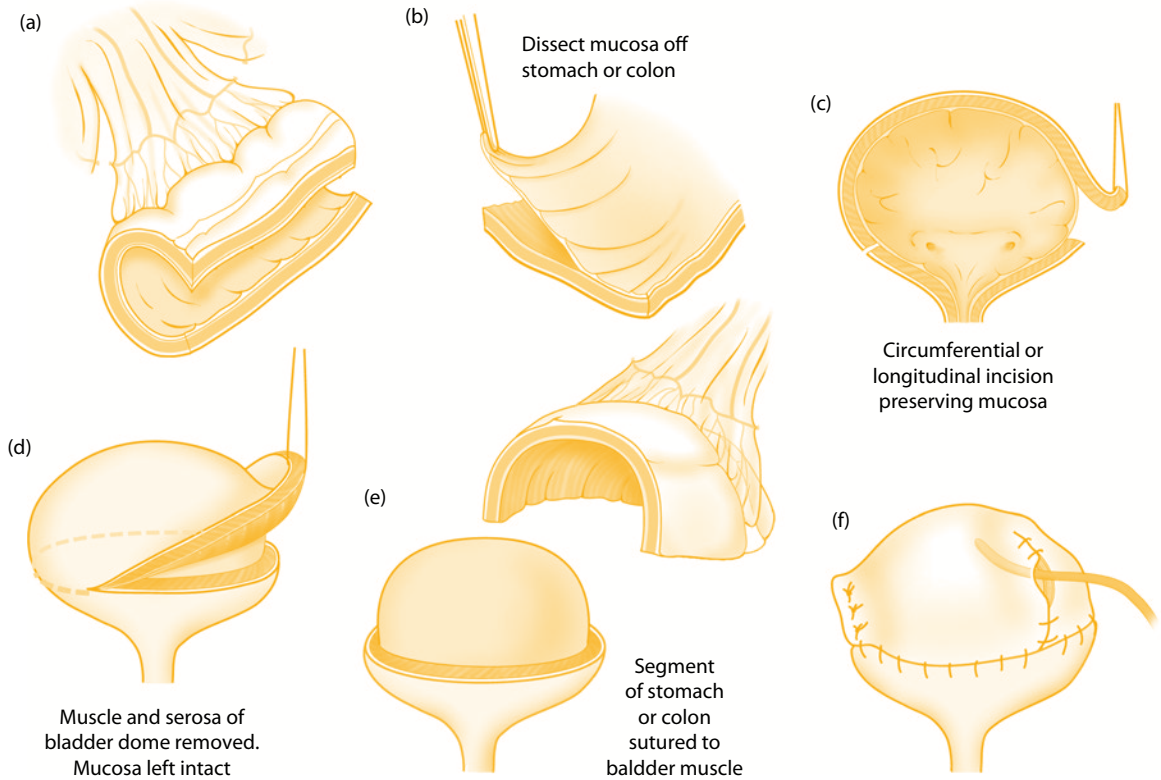

FIGURE 57.12 Seromuscular enterocystoplasty. (a) A portion of the stomach or colon is isolated. (b) The mucosa is removed with sharp dissection. (c and d) An autoaugmentation is then performed, resulting in an exposed diverticulum of bladder mucosa. (e) The demucosalized flap of the stomach or colon is laid on top of the exposed mucosa and anastomosed to the edges of bladder muscle. (f) A drain can be placed in between the flap and the mucosa to facilitate adherence of the two surfaces. (Adapted from Buson H. et al., *Urology*, 1994;44:743–8. With permission.)

in the submucosa) needs to be removed, in addition to the enteric mucosa, to prevent regrowth of intestinal mucosa and flap contracture,[192] while others have argued that preservation of the submucosa with the flap is necessary to prevent flap contracture during the immediate postoperative period.[193] Once the plane of dissection is established, removal of the mucosa can be accomplished with sharp dissection and intermittent use of electrocautery. Usually, the mucosa can be progressively peeled away from the underlying muscle once the proper plane has been established. Occlusion of the arterial blood supply during this dissection can be done to decrease blood loss and facilitate visualization.[194] Since some have postulated that the trauma of demucosalization is a factor that contributes to flap contracture, alternative methods of mucosa removal have been developed, including the use of an argon beam laser.[195] Alternatively, the bowel segment can be distended with a Foley balloon prior to detubularization and the seromuscular flap can be dissected off of the underlying mucosa from the outside.[196]

If the seromuscular enterocystoplasty is to be performed alone without autoaugmentation, the demucosalized flap is placed onto the bivalved bladder, as is routinely done for intestinocystoplasty. Postoperatively, some authors have suggested the need for diversion of urine from the bladder with externalized stents and distention of the augmented bladder with a silicone balloon for the first couple of weeks postoperatively to avoid flap contraction.[197]

If the seromuscular enterocystoplasty is to be combined with autoaugmentation, the flap is placed on top of the exposed mucosa following completion of the autoaugmentation, as described in the previous section. Adherence of the bladder mucosa to the raw surface of the seromuscular flap is felt to be critical to the long-term success of this operation. Several techniques have been suggested to facilitate this process. A small, flat Jackson–Pratt drain has been used to prevent the formation of a hematoma or seroma between the urothelium and the seromuscular flap that could prevent adherence between the two surfaces. Multiple mattress sutures can also be used to secure the flap to the native bladder urothelium. As with autoaugmentation, postoperative distension of the bladder with intermittent irrigation or constant distension of the bladder to 20–30 cmH_2O appears to be important for success. Carr et al.[194] have described the use of a Helmstein balloon in the bladder postoperatively to produce partial distension and compaction of the urothelium against the denuded muscle.

Results

Initial preliminary reports by Dewan and Gonzalez in both animal models and humans were encouraging.[188,189,198,199] In a series of 16 patients undergoing seromuscular colocystoplasty using sigmoid colon, bladder capacity was increased to almost 2.5 times the preoperative volume and

end filling pressures decreased by approximately 50%.[199] Dewan and Stefanek[198] reported on five patients undergoing seromuscular gastrocystoplasty. Four of the five patients had urodynamic evidence of improved bladder capacity and compliance during the first postoperative year. Despite these initial encouraging results, it is important to note that the follow-up in these early series was relatively short, and that approximately 25% of patients have eventually required a secondary operation due to either complications related to the seromuscular flap (contracture) or failure to adequately improve bladder capacity and/or compliance.

A subsequent report from Carr et al.[194] described 13 patients that underwent seromuscular gastrocystoplasty with variable success.[194] The mean follow-up was 50 months. Five patients had a good outcome and four had a fair outcome with regard to objective urodynamic and subjective clinical improvement. The remaining four patients had a poor result and required reaugmentation. Evaluation of preoperative urodynamic and radiographic data in these patients again demonstrated that it was not possible to predict preoperatively which patients would do well after seromuscular gastrocystoplasty.

More recent large series with long-term follow-up have been reported with more encouraging results. Lima et al.[197] reported on 129 patients that underwent seromuscular enterocystoplasty, of which 24 were done without concomitant autoaugmentation. Sigmoid was used in 104 cases, and ileum was used in the remaining 25. Median follow-up was 51 months. A 329% increase in bladder capacity was noted, and a sevenfold increase in bladder compliance. No significant mucus production was noted in any patient, and no cases of perforation were observed. Ten percent of patients did require reaugmentation. The authors attributed their improved success to several modifications in technique. This includes demucosalization of the seromuscular flap from the outside with use of an intraluminal Foley balloon during this important dissection and routine postoperative distention of the bladder and diversion of the urine for 2–3 weeks. Jednak et al.[200] have also reported favorable results in 32 patients. All were done in conjunction with autoaugmentation. Mean follow-up was 1.6 years. A near twofold increase in bladder capacity was noted with a 12.5% reaugmentation rate. A more recent report from the same group has also demonstrated the ability to combine seromuscular enterocystoplasty with placement of an artificial sphincter with no increase in the complication rate.

Recurrent or persistent intestinal mucosa has been found in several patients after seromuscular enterocystoplasty.[192,200] Whether this partial intestinal regrowth is progressive or clinically relevant remains to be determined. As mentioned above, it has been suggested and supported by animal studies that removal of the submucosa may prevent reepithelialization of the seromuscular flap with islands of native enteric mucosa.[192]

Ureterocystoplasty

The use of ureteral tissue for bladder augmentation was first described in 1992.[201,202] Since then, its use in children has become more popular.[203–205] For many reasons, native ureter is the best tissue available for augmentation cystoplasty. It is autologous, lined with urothelium, backed by muscle, distensible, and compliant. However, few patients in need of bladder augmentation have widely dilated ureters available for such use. Patients who are candidates for ureterocystoplasty should have either a nonfunctional renal unit that can be removed, making the ureter and renal pelvis available, or a functional renal unit that is associated with a massively dilated, tortuous, and elongated ureter.[203,206] The lower ureter can then be used for augmentation while kidney drainage is reestablished either by reimplantation of the straightened upper ureter into the bladder or by transureteroureterostomy.

One of the challenges that one faces in selecting the appropriate patient for ureterocystoplasty is determination of whether the ureter that is to be used is going to be adequate enough for successful augmentation. Recent clinical experience and long-term urodynamic follow-up suggests that the detubularized and reconstructed ureter following ureterocystoplasty remains compliant, but that the overall compliance, distensibility, and volume may not increase significantly compared with the dilated intact ureter in its preoperative state. Thus, postoperative urodynamic studies in a patient that has a refluxing ureter that was used for ureterocystoplasty may not show a significant increase in volume and compliance of the augmented bladder compared with preoperative studies (when the ureter was refluxing and intact).[207] However, if the ureter that is to be used is not refluxing, then improvement in urodynamics following ureterocystoplasty would be expected and may be directly related to the degree of ureteral dilatation that is present preoperatively. Given this, preoperative urodynamic studies can be very valuable in select patients in predicting success or failure following ureterocystoplasty, especially in the setting of refluxing ureter.

Ureterocystoplasty can also be appropriate in patients with end-stage renal failure on dialysis who are awaiting transplantation and are in need of augmentation owing to bladder dysfunction. As is the case with conventional intestinocystoplasty, the augmented bladder following ureterocystoplasty and subsequent transplantation has been shown to function adequately.[208]

Anatomy and Physiology

Preservation of the ureteral blood supply is paramount when performing ureterocystoplasty. The normal ureter receives its blood supply from branches of numerous vessels, including the aorta and renal, gonadal, and common iliac arteries (Figure 57.13). The upper ureter receives its blood supply medially, while the lower ureter receives it posterolaterally. There are extensive anastamosing plexuses in the adventitia of the ureter that are important to preserve if viability of the ureter is to be maintained. Careful attention to these vessels allows for long segments of ureter to be mobilized without vascular compromise. Ureteral urothelium is contiguous with the urothelium from the bladder and has similar physiologic characteristics. Peristalsis of the ureter depends on autonomic innervation and input from intrinsic pacemaker sites in the minor calyces of the renal collecting system.[209] Although the ureter is detubularized and its inherent innervation is

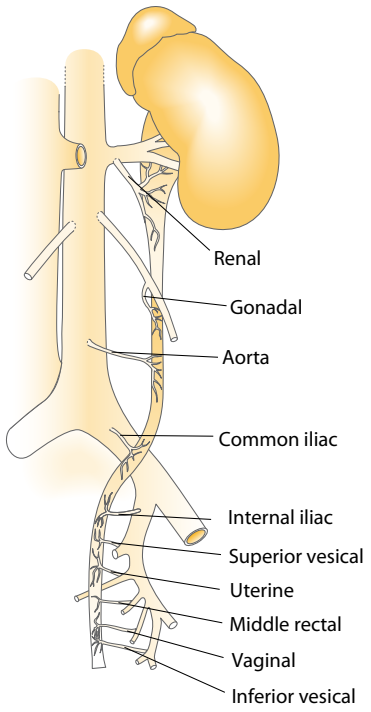

FIGURE 57.13 Arterial blood supply to the ureter. (Adapted from Lindner H. *Clinical Anatomy*, Norwalk, CT: Appleton and Lange, 1989. With permission.)

disrupted with ureterocystoplasty, it appears that the ureteral tissue still maintains some ability to contract.

Advantages and Disadvantages

There are several advantages in using the ureter for augmentation. As is the case with autoaugmentation, the major advantage of ureterocystoplasty is that the native urothelium is preserved, thereby avoiding the specific potential problems associated with the use of the bowel. Unlike some cases following autoaugmention, the full-thickness opened ureter does not tend to shrink with time, unless the vascular supply is compromised. In patients with end-stage renal disease, the procedure can be performed extraperitoneally, thus preserving the peritoneum for future peritoneal dialysis. Alternatively, it can also be performed with laparoscopic assistance for the nephrectomy and upper ureter mobilization.[210] When needed, concomitant procedures in the bladder may also be performed. It seems likely that the risk of tumor formation will be avoided, and perforation of the augmented bladder may be less probable. However, long-term follow-up will be needed to confirm these possibilities.[203] Finally, there is increased potential for spontaneous voiding postoperatively, especially in patients who are able to empty their bladders adequately preoperatively.

The main disadvantage of ureterocystoplasty is that it is only applicable in a minority of patients. More recently, the use of ureterocystoplasty has been expanded in an attempt to take advantage of this valuable tissue and make it available to more surgical candidates. Its use has been reported in patients with a duplex system in which either the upper or lower pole is nonfunctioning.[211] In patients with a duplex system and a dilated ureter in conjunction with a functioning renal segment, drainage of that segment can be accomplished with an ipsilateral pyeloureterostomy or a ureteropyelostomy with preservation of the distal portion of the ureter for augmentation. Ahmed et al.[212] also described the tandem use of bilateral megaureters for ureterocystoplasty.

Efforts are being made to produce dilated ureters in an attempt to make ureterocystoplasty available to more patients. Lailas et al.[213] have demonstrated in a rabbit model that a temporary cutaneous ureterostomy can be used to perform hydrostatic distension of the ureter with subsequent successful ureterocystoplasty. Others have reported that placement of a tissue expander in pig ureters adequately dilates the ureter.[214,215]

Surgical Technique

Patients undergoing ureterocystoplasty should have a full bowel preparation and sterilization preoperatively in case the ureter is not suitable for augmentation. The procedure can be performed either through a midline incision with a transperitoneal approach to the urinary tract or via two incisions, such as is used for nephroureterectomy.[216] The latter approach is extraperitoneal. This may be advantageous in patients with severe renal insufficiency who may subsequently require peritoneal dialysis. A nephrectomy is performed initially, preserving the renal pelvis. The upper portion of the ureter and renal pelvis are then mobilized (Figure 57.14). Efforts should

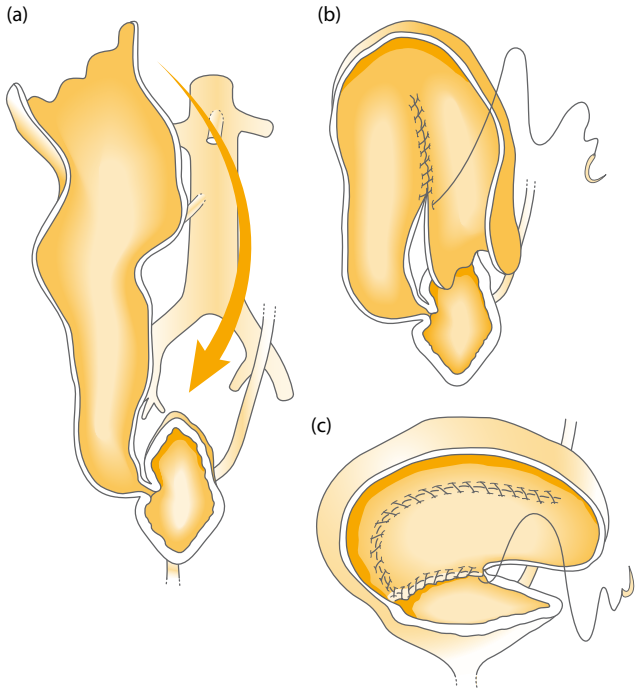

FIGURE 57.14 Ureterocystoplasty. A standard nephrectomy is performed with preservation of the renal pelvis. (a) The proximal ureter is mobilized with preservation of the medial blood supply. (b) The ureter is then detubularized with the incision for detubularization connecting with the off-center cystostomy. (c) The ureter is folded on itself and anastomosed to the opened bladder.

be made to preserve as much renal pelvis as possible since this increases the surface area of the augmentation. One should include any available periureteral tissue to protect the network of vessels within the ureteral adventitia. Although the blood supply from the lower ureter (which is derived posterolaterally) can maintain the viability of the upper ureter via this adventitial network, efforts should also be made to preserve collaterals from the gonadal vessels and the main renal vessels. These vessels supply the renal pelvis and upper ureter directly, and their preservation helps to ensure adequate vascular supply to the upper portion of the ureter. As Churchill et al.[217] have noted, preservation of the upper ureteral blood supply is most important when previous reconstructive surgery has compromised the collaterals involving the distal ureter.

Following mobilization of the renal pelvis and ureter, the ureter is detubularized and reconfigured to form a patch. The bladder is then opened. The bladder incision extends from the ipsilateral ureteral orifice to the contralateral ventral quadrant of the bladder. The incision is carried through the ipsilateral ureteral orifice so that it unroofs the intravesical ureter and meets the detubularization incision in the ureter. This allows the bladder to be opened sufficiently for ureterocystoplasty without much risk of an hourglass deformity. Alternatively, to preserve vascularity, the incision can stop short of the orifice, maintaining the normal configuration of the distal ureter for a few centimeters.[202] Once the bladder is adequately opened, the reconfigured ureteral segment is sutured to the defect in the bladder, creating a wide anastomosis. Prior to closure, a suprapubic tube is placed through the native bladder, and left indwelling for 2–3 weeks. Postoperative care is essentially the same as for routine enterocystoplasty except that daily irrigation for mucus is not required.

Results

Since its original description in 1992, widespread experience has been gained with ureterocystoplasty. Early reports demonstrating its efficacy led to increased enthusiasm for this technique and a desire to use the ureter instead of intestinal segments whenever adequate ureteral tissue is available. Churchill et al.[203] initially reported on 16 patients in which there was a 218% increase in bladder capacity, a 284% increase in pressure-specific bladder capacity, and a 227% increase in bladder compliance. In a follow-up to this study, Landau et al.[218] compared the urodynamic results between patients treated with ileocystoplasty and those with ureterocystoplasty. They reported no significant differences in the postoperative mean increase in bladder capacity and pressure-specific bladder volume. Both procedures resulted in excellent functional results. Hitchcock et al.[219] described similar excellent short-term results in eight patients.

Subsequent reports have also demonstrated that ureterocystoplasty can be an effective augmentation procedure but have further clarified which patients are most appropriate for the procedure and what amount of ureter is needed for success. Pascual et al.[220] described 22 patients in which only the distal ureter of a single ureter was utilized for augmentation. While increases in capacity and improvement in compliance were noted, only half of the patients reached the expected age capacity of the bladder, and the overall results were less successful than those of other reported previous series in which the entire ureter was utilized. In the largest series to date, Husmann et al.[207] reported on 64 patients from multiple institutions. In 40 of the patients, augmentation was performed with a complete single or double collecting system. In 9/40 patients, reflux was not present and postoperative success directly correlated with a preoperative ureteral diameter of greater than 1.5 cm. In the remaining 31 patients, reflux was present preoperatively. In these refluxing patients, if the system on preoperative urodynamics demonstrated only mild noncompliance (greater than 20 mL/cm water), then ureterocystoplasty improved compliance onefold and was adequate. However, if the system preoperatively demonstrated poor compliance, then ureterocystoplasty did not adequately improve capacity and compliance, resulting in 81% of patients having either undergone or being considered for reaugmentation.

Collectively, these results suggest that the ideal patient for ureterocystoplasty is one with a massively dilated ureter in which most or all of the ureter can be used for augmentation purposes. If reflux is present preoperatively, then preoperative urodynamics can be predictive of future success. If a poorly compliant system is present in the setting of a dilated refluxing ureter, then failure and the need for reaugmentation are likely. Novel techniques to make ureterocystoplasty more readily available for patients that do not have massive dilatation of the ureter are currently being investigated.

TISSUE-ENGINEERED BLADDER

The complications associated with using various portions of the gastrointestinal tract for genitourinary reconstruction in both adults and children who have been described in this chapter have stimulated the development of tissue engineering techniques for bladder reconstruction through bladder regeneration. Current research efforts are focused on the development of biodegradable materials that are well characterized with predictable behavior that can be used as alternatives to gastrointestinal segments for bladder reconstruction. Although attempts at bladder reconstruction via bladder regeneration are not new,[221] the major obstacle has been the unavailability of a biomaterial, either permanent or biodegradable, that will function as a suitable scaffold to allow the process of regeneration to occur either naturally or with the addition of cultured cells. The ideal graft material is one that would be replaced by the host tissue, provide a low-pressure reservoir, and serve as a scaffold for regeneration of the bladder wall with normal functional characteristics. If a suitable graft material were developed, the need for autogenous tissue and the associated complications of intestinal segments could be eliminated. Currently, two types of tissue engineering technology have been shown to induce bladder regeneration in preliminary studies. These are the “unseeded” and “seeded” technologies.

Unseeded Technology

The first technique currently being investigated for bladder regeneration is unseeded technology. This involves the use of tissue matrix grafts that are biodegradable, acellular, collagen based, autologous, or xenogenic.[222–224] This technology involves placement of the graft into the wall of the host bladder. The body then provides the needed environment for subsequent cell growth and tissue generation. This represents an unseeded bladder-regenerating process.

Historically, the major obstacle to unseeded tissue engineering technology has been the inability to develop an optimal biomaterial that will act as a suitable scaffold for the "natural" process of regeneration. Synthetic nonbiodegradable materials such as silicone, rubber, polytetrafluoroethylene, and polypropylene have been tried with unsuccessful results because of host–foreign body reactions.[225–229] As a consequence of these failures with nonbiodegradable materials, synthetic biodegradable materials were developed. It was anticipated that these grafts will allow the host bladder adequate time for regeneration but dissolve before the onset of foreign body reactions. These materials have been used experimentally and have shown less graft encrustation and fewer infectious complications than nonbiodegradable materials. However, graft shrinkage still limits the potential clinical utility of these materials.[230] Nonsynthetic biodegradable materials, such as placenta, amnion, and pericardium, have been investigated and have shown a clear ability to host bladder regeneration.[231–234] However, despite initial encouraging laboratory results, none of these materials have been found to be suitable for clinical use.

More recently, new types of biodegradable material have been developed that have shown tremendous potential for the induction of bladder regeneration with unseeded tissue engineering technology. These materials are acellular extracellular matrix (ECM) grafts that are derived from various organs. The graft is made acellular by a mechanical process that lyses the cells and/or by detergent and enzymatic extraction. These types of ECM grafts have been derived from full-thickness bladder and stomach and the submucosal layer of the small intestine.[222,235,236]

The most thoroughly studied collagen-based ECM graft for bladder augmentation and urinary reconstruction using unseeded technology is the small intestinal submucosa (SIS).[237] SIS is a xenogenic membrane derived from pig small intestine in which the mucosa is mechanically removed from the inner surface and the serosa and muscularis are mechanically removed from the outer surface. This results in a thin, translucent membrane (0.1 mm wall thickness) composed mainly of the submucosal layer of the intestinal wall. Production of SIS is reminiscent of the manufacture of sausage casing. This unique material has been shown to function well with rapid replacement by native tissues and evidence of tissue-specific regeneration.[238–240]

SIS has been shown to be nonimmunogenic, with more than 1000 cross-species transplants and direct challenge testing elucidating no response.[241–243] In addition, SIS is unique from other biomaterials that have been studied thus far in that it contains a combination of active intrinsic growth factors, cytokines, structural proteins, glycoproteins, and proteoglycans that may assist in cell migration, cell-to-cell interaction, and cell growth and differentiation during the regenerative process.[244–246]

SIS grafts have been shown to promote full-thickness bladder regeneration in both rat and canine animal models.[247] The regenerated bladder tissue is composed of all three layers of the normal bladder wall (urothelium, smooth muscle, and serosa). In addition, the regenerated segment is contractile, compliant, and functionally innervated. Urodynamic studies in a long-term canine augmentation model have demonstrated that the SIS augmented bladder maintains normal bladder capacity and compliance for at least 15 months postoperatively.[248] In vitro muscle strip studies on the regenerated portions of the bladders also demonstrate contractility and compliance that is similar to that of the normal bladder.[249] In these rat and canine studies, a partial cystectomy model was used for SIS augmentation in which $\geq$50% of the native bladder still remained as a bladder template. Subsequent work with a near-total cystectomy model in which a more severe defect is created ($\geq$90% of the bladder removed) resulted in less promising results. Severe fibrosis, adhesions, calcification, and graft contraction were noted. These discordant results in a near-total cystectomy model were likely secondary to poor neovascularization and resultant tissue ischemia in the central portion of the SIS graft. Therefore, the ability of unseeded SIS to induce functional augmentation of the bladder may in part be limited to the size of the graft and/or percentage of the native bladder that remains as a template for the support of neovascularization of the regenerating tissue.[294]

In all the animal studies utilizing SIS that have performed thus far, there has always been a variable degree of regeneration noted. This is likely due to the fact that SIS is biologic material that is derived from different segments of the small bowel, and that the intrinsic growth factors and structural makeup of the bowel may be variable depending on the bowel segment and animal that it is harvested from. This notion is supported by additional work by Kropp et al.[250] that has shown that bladder regeneration is more uniformly successful when using SIS that is harvested from the distal ileum from a 3-year-old sow as compared with the proximal jejunal segment from the same-age sow.[251] Additional work is now being done to develop improved processing techniques that will result in a more uniform type of SIS that will be more consistent in its regenerative capabilities.

Acellular ECM grafts to SIS have also been shown to induce bladder regeneration. Preliminary work by Sutherland et al.[224] and Piechota et al.[270] demonstrated that successful morphologic and functional regeneration of the rat urinary bladder can be accomplished with homologous bladder acellular matrix grafts (BAMGs). Reddy et al.[236] also reported on partial bladder substitution with porcine bladder acellular matrix allografts (BAMAs) in a porcine model. They demonstrated that the regenerated urothelium with BAMAs was multilayered and that there was also histologic evidence of organized smooth muscle regeneration and neoangiogenesis at 30 days.

The above experience with SIS and other similar ECM-derived biomaterials clearly demonstrates that bladder regeneration using unseeded tissue engineering technology is feasible. However, there are still several limitations that have prevented this technology from progressing to clinical implementation. Commercial manufacturing that

yields predictable biological activity has not yet consistently been achieved. In addition, there is increased central scarring with contraction in larger grafts that is likely in part due to insufficient neovascularization and resultant graft fibrosis. With greater understanding of the individual composition of the various biomaterials,[252,253] the cell-to-cell interactions, and the growth factors[224,254–256] that are involved in the bladder regenerative process that promote adequate ingrowth of native cells and neovascularization, the ability to produce a more uniform biodegradable graft may be realized. Thus, additional research is still needed to bring us closer to having an off-the-shelf, acellular, clinically available product for bladder augmentation.

Seeded Technology

The second type of tissue engineering technology, the seeded technique, involves the use of biodegradable materials that act as cell delivery vehicles for cultured cells from the patient. This technique has been applied to the urinary bladder. Initially, this process is begun by harvesting native bladder tissue for the establishment and expansion of primary cultures of both bladder smooth muscle and epithelial cells. Cilento et al.[257] demonstrated that it is possible to expand a bladder epithelial cell culture from a single biopsy specimen such that the cultured cells could cover a surface area of more than 400 m^2 within 8 weeks. Once the cells are grown, they are seeded on a biodegradable membrane in vitro and then transplanted back into the host for continuation of the regenerative process. Atala et al.[258] demonstrated the successful use of nonwoven polyglycolic acid (PGA) polymer sheets that allow the seeded growth of urothelial and smooth muscle cells. Further work demonstrated that these cell–polymer constructs could then be implanted into athymic mice, with the subsequent formation of organized layers of bladder epithelial and smooth muscle cells. Yoo et al.[259] and Oberpenning et al.[260] reported on the feasibility of dog bladder augmentation using allogenic bladder submucosa or PGA polymers seeded with urothelial and smooth muscle cells. Organized bladder histology was noted in the regenerated bladder tissue. More importantly, the regenerated bladder tissue was found to increase bladder capacity and was urodynamically compliant. Based on these encouraging results, more novel types of biodegradable scaffolds other than PGA polymers are now being evaluated both in vitro and in vivo for their potential use utilizing seeded technology.[261,262,292]

The demonstration that seeded technology can facilitate regeneration of functional bladder tissue in a large animal model provided the foundation for a landmark clinical trial that utilized autologous engineered bladder tissue as an alternative for conventional enterocystoplasty. Atala and colleagues performed augmentation cystoplasty on seven patients with spina bifida. PGA composite grafts seeded with autologous urothelial and smooth muscle cells were successfully implanted in these patients with additional utilization of an omental wrap around the seeded graft to aid in vascularization.[263] Although histological data at the 5-year follow-up displayed a trilayered architecture composed of urothelium, submucosa, and muscle, there was significant variability seen in the results with regard to the functional parameters of capacity, compliance, and leak point pressure. Only one of seven patients had an increase in bladder capacity and improvement in compliance similar to that which is routinely seen with conventional enterocystoplasty. This increase in bladder capacity took 5 years and was not observed in the first few years after augmentation. The reasons for this delayed response are not clear. In addition, patients were not able to spontaneously void and continued to require intermittent catheterization. This preliminary experience in humans with a neurogenic bladder clearly demonstrates that seeded technology can facilitate bladder regeneration to some degree. However, the results observed thus far do not compare favorably with conventional enterocystoplasty. Thus, additional research is needed to elucidate the reasons for the inferior results noted in this human trial compared with previous animal studies before it can be considered for clinical use.

Future direction

Although both unseeded and seeded technologies have been shown to be successful in animal models, the failure of these technologies to be successfully applied clinically demonstrates that there is much work to be done before bladder tissue engineering can be realized as a viable alternative to conventional bladder augmentation.[263] Three challenges that have been identified that currently limit our ability to be successful are (1) deficiencies in scaffold design, (2) use of an appropriate cell source for seeding, and (3) lack of adequate neovascularization of the regenerating graft. Current research is now being focused on these vital issues and is discussed next.

Scaffold Design

Biologic scaffolds have the advantage of their inherent content, in which intrinsic growth factors facilitate new tissue growth. However, as previously discussed, the inherent variability in these biologic materials is a hindrance. Synthetic materials are more consistent in content but lack biologic activity. Therefore, recent research efforts have focused on developing materials that are consistent in content yet still biologically active. Utilizing advancements in nanotechnology, synthetically derived and immunotolerant biomaterials are now being designed to provide the necessary structural and biological properties required to induce a seeded population of cells to successfully contribute to the dynamic process of bladder regeneration.[286] An example of this is the use of self-assembling peptide amphiphile (PA) systems. PAs are nanodesigned for self-assembly through the covalent attachment of hydrophobic (alkyl) and highly charged hydrophilic (peptidic) segments. The terminal end of each PA can include a biologically relevant epitope for signaling cells, binding other biomolecules, or yielding other functionality.[282] The PAs can then be designed to bind specific growth factors that can then be released locally in a time-dependent fashion to facilitate cell growth and differentiation. Harrington et al. have utilized this strategy to develop synthetic scaffolds coated with branched self-assembling PAs that can bind and release basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF).[282,283] When these nanodesigned scaffolds were seeded with bladder cells, in vitro and in vivo studies

demonstrated the ability to modulate cell proliferation, cell adhesion, and matrix production.

Similar efforts have also been made to alter biodegradable scaffolds to alter structural content and enhance their regenerative properties with both unseeded and seeded technology. SIS and other ECM-based scaffolds have been coated with hyaluronic acid and/or poly(lactic-co-glycolic) acid polymers that can then impact cell adhesion, cell contraction, and permeability of the regenerating scaffold.[287] The latter could also positively impact the regenerative process in the bladder by limiting extravasation of urine and thereby reducing inflammation. Current efforts are now being directed at binding different bioactive nanoparticles in various manners to biodegradable scaffolds to better facilitate the regenerative process.[285,288,289] The ability to improve on current scaffold designs to enhance biologic response in a consistent fashion will be an integral component to enhance our ability to direct cell growth and activity during the regenerative process.

Cell Source

Despite the successful use of autologous bladder cells in seeded technology, there are significant concerns regarding the functional characteristics of the cells harvested from a dysfunctional or neurogenic bladder.[20,264,286] (Matoka and Cheng 2009). In vitro work has suggested that when bladder cells are harvested from a neuropathic bladder, they retain important functional differences, and that conversion to a normal phenotype when they are seeded on scaffolds may not occur.[249,278,280] These findings suggest that one of the plausible reasons that clinical trials with seeded technology failed to have consistent results is because the autologous *neuropathic* source of the cells did not have the capacity to facilitate regeneration of *normal* tissue. Therefore, emphasis has now been placed on exploring the possible use of both pluripotent and multipotent autologously derived stem cells that are capable of self-renewal and tissue-specific differentiation but will not illicit an unwanted immune response.[277] The potential use of stem cells in all disciplines of regenerative medicine has been heavily investigated. In the setting of bladder regeneration, the use of bone marrow–derived stem cells has been found to be particularly useful. Bone marrow–derived stromal cells have been shown to have the ability to differentiate into bone, fat, cartilage, muscle, and other lineages, as well as nonmesenchymal tissue cell types, such as endodermal and neural cells. Bone marrow stromal cells and mesenchymal stem cells (MSCs) derived from the bone marrow have both been successfully used as alternatives to autologous bladder cells for seeded technology.[291,293] These cells are easily harvested and highly proliferative, and undergo a relatively wide range of differentiation. When purified MSCs have been utilized with seeded technology for bladder augmentation in rodent models, bladder regeneration was noted that was indistinguishable from that obtained with autologous bladder cells.[279,292] This suggests that the MSCs have the capacity to differentiate into bladder smooth muscle. Recent work with seeded MSCs in a primate bladder augmentation model demonstrated that the seeded MSCs actively participate in the regenerative process, in addition to their role as a homing device for native cells.[290] Other sources of non–bone marrow–derived stem cells have also been shown to be plausible for use with seeded technology.[281,284] Clearly, the utilization of biocompatible scaffolds in combination with autologous stem cells for regenerative purposes in urology is an important advancement in the field of tissue engineering that may allow us to circumvent the use of abnormal cells from the host organ.

Neovascularization

Long-term survival of unseeded or seeded scaffolds depends on the development of adequate vascularization. A major hurdle that needs to be addressed with large grafts is the inability to provide adequate neovascularization to the regenerating tissue, which subsequently results in ischemia and tissue fibrosis.[285] A proposed strategy to overcome this problem is to create a scaffold or seeded graft for augmentation that already has a partially or fully intact autologous blood supply.[265–268] Alternatively, one can also create an angiogenic microenvironment in the regenerating tissue to facilitate improved vessel formation. This can be accomplished with the use of seeded vascular progenitor cells and/or vasculogenic growth factors. Sharma et al. has demonstrated that when both bFGF and VEGF are integrated into a synthetically derived scaffold, enhanced local angiogenesis can be observed.[289] In addition, it has been proposed that the use of MSCs in combination with CD34+/CD133+ endothelial progenitor cells (EPCs) may facilitate new vessel formation that further promotes improved neovascularization and muscle formation in the regenerated tissue.[269,290–292] These and other new strategies to facilitate adequate blood supply to the regenerating tissue may well be the most important issue that needs to be addressed if we are going to be successful in the clinical application of tissue engineering technology for bladder augmentation.

Further advancements in scaffold design, alternative cell sources for seeding, and measures to promote neovascularization will be areas of intense future research aimed at improving our current ability to provide large pieces of regenerated bladder tissue for augmentation purposes. However, before clinical application of this technology can be considered, additional work is still needed. At this point in time, conventional enterocystoplasty still represents the gold standard for augmentation of the neurogenic bladder. However, it is clear that bladder regeneration is possible using both unseeded and seeded tissue engineering technologies. Hopefully, further advances in current techniques will eventually revolutionize urologic reconstructive surgery to the point where tissue-engineered bladder will be offered as first-line therapy.

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CHAPTER 58

Urinary Diversion

Peter D. Metcalfe and Richard C. Rink

INTRODUCTION

Efforts over the past generation have resulted in significant advances in the care of our most complex patients. Medical care has progressed to where renal insufficiency is rare and continence can be expected. Aggressive medical and surgical management often begins in childhood and is adapted to the clinical, individual, and social situation of the patient and family throughout their life. Therefore, while the majority of our patients and their families may desire complex reconstructions aimed at urinary continence, the need for simple and effective urinary diversion will always be required.

The best patient care will always demand judicious use of the full spectrum of urinary diversion, and this chapter acknowledges a broad array of diversion options. Some urologic scenarios still result in severe urinary obstruction in the premature neonate or critically ill, and effective, temporary diversion is required.[1,2] Furthermore, simple and effective diversion is still required for long-term care patients unwilling or unable to perform the necessary maintenance required of a continent urinary reservoir (CUR).[228] This chapter focuses on a multitude of temporary and permanent, historic and contemporary diversions, with an emphasis on surgical indications, techniques, and complications.

Temporary Urinary Diversion

Temporary Intubated Diversions

Urethral Catheter

The most frequently used urinary diversion is the Foley catheter. The most critical scenario occurs after the birth of a patient suspected to have posterior urethral valves (PUVs). Foley catheters (6 or 8 Fr) are readily available and usually easily inserted in the neonate. Sizing of the catheter is relatively accurate based on the patient's age (Table 58.1).[3]

Many current nursing policies recommend against the routine use of feeding tubes, due to their propensity to knot inside the bladder and result in traumatic extubation (Figure 58.1).[4,5]

Immediate catheterization of the newborn suspected of PUVs allows for stabilization of the patient until he or she is well enough to undergo VCUG and valve ablation. If the catheter is difficult to pass, a small lacrimal duct probe or manual guidance with a finger in the rectum may be helpful. Furthermore, it may be helpful to place a finger in the rectum to elevate and straighten the prostatic urethra during catheter placement. Occasionally, a bedside cystoscopy and placement of a council catheter over a guidewire are required, especially after a traumatic catheterization. After a difficult catheterization, it is appropriate to obtain an abdominal radiograph, after injecting a small amount of contrast through the catheter, or pelvic ultrasound, to ensure its proper position in the bladder.

Patients who suffer from chronic urinary retention, i.e., those with a spinal dysraphism, posterior valves, or other congenital anomalies, may benefit from intermittent catheterization, as opposed to the long-term use of an indwelling catheter. Clean intermittent catheterization (CIC) is an excellent option for children with chronic urinary retention and has proven to be safe in even the neonate.[6] However, the benefits in the short term need to be weighed against the difficulties with cooperation and the potential emotional trauma in the elementary school-aged patient.

Complications of urethral catheters in children are usually related to improper placement or prolonged use, and include urethral injury (Figure 58.1), urethritis or meatitis, urinary tract infection (UTI), urethral stricture, and bladder stones. Unfortunately, these are quite common, but they should be minimal with appropriate teaching and care and minimization of the use of urethral catheters.

Suprapubic Cystotomy

In rare circumstances, a urethral catheter is contraindicated or cannot be placed, and a suprapubic cystotomy tube can provide short- or long-term bladder drainage. A cystotomy is very useful in the infant or child with urethral trauma or following a reconstructive procedure for epispadias or complex hypospadias in the older child. Many excellent percutaneous kits are available to facilitate placement; however, in children this usually mandates a general anesthetic. A full bladder is an absolute prerequisite to percutaneous catheter placement and can be confirmed sonographically or cystoscopically. When attempting to place a suprapubic tube in the awake child, conscious sedation and infiltration of the skin and fascia with 1% lidocaine can be used to prevent anxiety and pain. It is helpful to establish the distance from the skin to the bladder lumen with a small needle to prevent injury to structures posterior to the bladder. The trocar is passed with gentle pressure until urine is obtained, and the catheter is passed 1–2 cm beyond the trocar. Alternatively, the percutaneous cystotomy tube and obturator needle are passed together into the bladder until urine is obtained,

TABLE 58.1 Approximate catheter size per patient age

Neonate	1500–2500 gm	6 Fr
0–6 months	3.5–7.5 kg	6 Fr
1 year	10 kg	6–8 Fr
2 year	12 kg	8 Fr
3 year	14 kg	8–10 Fr
5 year	18 kg	10 Fr
6 year	21 kg	10 Fr
8 year	27 kg	10–12 Fr
12 year	>27 kg	12–14 Fr

and then the catheter is advanced over the obturator. A recently described technique using the light from a flexible cystoscope to help localize the position of the bladder dome may allow percutaneous tube cystotomy in the more difficult cases.[7] In children with a history of prior reconstruction bladder surgery, it is often safest to use the site of a prior suprapubic tract that is fixed to the posterior abdominal fascia to place the suprapubic tube. The catheter is fixed to the skin with permanent suture. Suprapubic catheters tubes are intended for temporary bladder drainage, as long-term use has been associated with bladder wall thickening and contracture, UTI, bladder stones, and upper urinary tract dilation.[8,9]

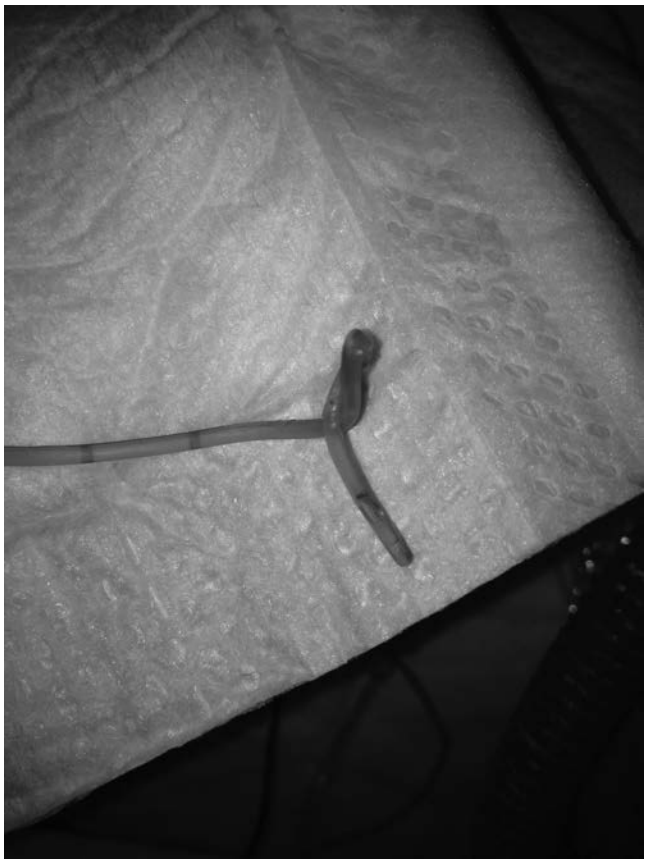

FIGURE 58.1 Photograph of 5 Fr feeding tube that had become knotted in the bladder of a neonate. Many nursing policies counsel against the use of feeding tubes as urinary catheters.

Open Cystotomy Tube

Because of the relative ease and safety of percutaneous cystotomy tube placement, open suprapubic tube placement is rarely used except in the context of a more extensive reconstructive procedure, or for placement of a large-bore drainage tube following urethral or bladder trauma. Another indication for the open technique is in a patient that has had prior extensive pelvic procedures that may have resulted in bowel adhesions to the anterior dome of the bladder.

With the patient in the supine position, the prevesical space is exposed using either a low transverse abdominal incision or a low vertical midline incision for those that may later undergo a transabdominal reconstructive procedure. After mobilizing the bladder dome, stay sutures are placed and a small cystotomy is made. The catheter is first brought through a small skin incision and then through the rectus fascia and muscle. After the tube has been placed in the bladder, it is pulled to the dome of the bladder and secured with a purse-string suture at the bladder. Bladder muscle adjacent to the tube is secured to the posterior fascial wall with absorbable suture, and the suprapubic tube is sutured to the skin.

Ureteral Stents

Ureteral stents are frequently used for temporary upper tract drainage following reconstruction, trauma, or stone surgery in children. There are two general options available, either an entirely internal stent or an external ureteral stent with one end brought out through the skin, urethra, or flank. External stents offer the benefits of not requiring an anesthetic for removal, being easily irrigated to prevent and treat internal obstruction, and having a miniscule risk of proximal migration. Problems that can be associated with internal JJ stents in children[10] include

- Obstruction
- Encrustation or stone formation
- Infection
- Proximal migration
- Stent fragmentation
- Discomfort or bladder spasms
- Requirement of anesthesia for removal of stent
- Hematuria

Internal JJ stents can be placed either at the time of open surgery, endoscopically, or by means of an antegrade approach through a percutaneous nephrostomy tract. Endoscopic placement of an internal stent may require fluoroscopy placement if the stent or "pusher" will not pass through the smaller size of the working port of pediatric cystoscopies. However, improvements are continuous, and most of our equipment can pass though the 5 Fr channels required for endoscopic correction of vesicoureteral reflux.

Percutaneous Nephrostomy Tubes

Improvements in the expertise and availability of pediatric interventional radiologists has led to percutaneous nephrostomy tube drainage almost completely replacing the need for open nephrostomy tube placement in children. Indications for nephrostomy tube drainage in

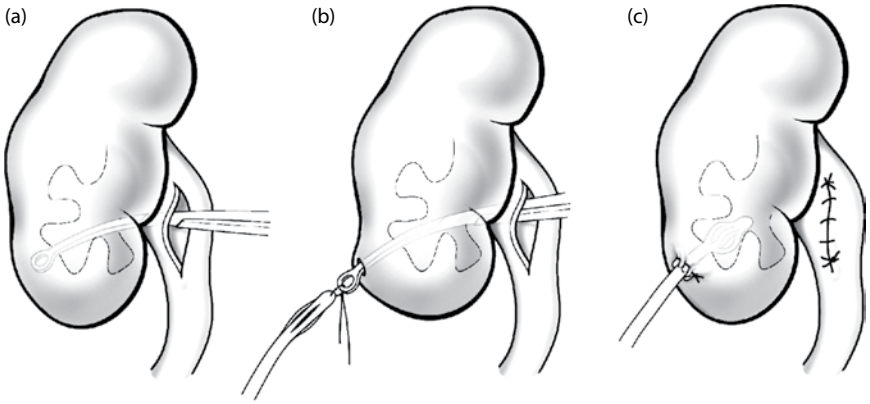

FIGURE 58.2 Technique for open nephrostomy. (a) Small Randall forceps or a right-angle clamp is passed through an inferior calyx via a small pyelotomy incision. (b) The renal capsule is incised with electrocautery, and the catheter is advanced into the calyx. The catheter is secured to the renal capsule with absorbable suture. (c) The pyelotomy is closed with either running or interrupted, absorbable suture.

children include obstruction, renal or ureteral calculi, pyonephrosis, and fungal bezoar, or for a diagnostic Whitaker study. Although general anesthesia will often be required in the young or uncooperative child, the procedure can frequently be performed with sedation only,[11] and has been performed with just local anesthesia in small neonates in the intensive care unit.[12] The technique most commonly used is the Seldinger technique. Under radiographic guidance, a small needle is placed into the renal pelvis, a guidewire is then passed into the renal pelvis, and the tract is dilated until a nephrostomy tube can be easily advanced. Several types of nephrostomy tubes are commercially available, most of which rely on a "pigtail" curl to maintain their position within the renal pelvis. It is critical that broad-spectrum intravenous antibiotics be initiated before tube placement, especially in the child with obstruction and infection, to prevent urosepsis. Complications directly related to the procedure are rare[13,14] and include

- Hemorrhage
- Urosepsis
- Arteriovenous fistula or pseudoaneurysm
- Urinary extravasation
- Pneumothorax
- Bowel injury
- Air embolism

Percutaneous nephrostomy tube placement and irrigation with antifungal agents has become the first-line therapy for neonates with obstructing fungal bezoars.[15–18] In addition to draining the obstruction and providing access for intermittent irrigation of the obstructed collecting system, the fungal ball can be fragmented with the guidewire at the time of tube placement, which will lead to more rapid clearance of the fungal debris.

Open Nephrostomy Tube

Open nephrostomy tube placement is rarely necessary, and only utilized when nephrostomy is technically not possible or carries an unacceptable risk. High-risk conditions include a low platelet count, a solitary kidney, an abnormal renal position following a complicated reconstruction of the renal pelvis, and exploration for renal trauma when significant injury to the ureter or pelvis has occurred. The kidney is exposed through a flank incision and mobilized until the renal pelvis is identified. Stay sutures are placed, and the renal pelvis is opened. A clamp is placed into an inferior calyx. A small nephrotomy is made, and the Malecot catheter is advanced into the renal pelvis as shown in Figure 58.2. The catheter is secured to the renal capsule with a purse-string chromic suture. The nephrostomy tube is brought out through a stab incision in the skin and secured. A small Penrose drain is left in the renal fossa. Some newer catheters come preassembled as either simple nephrostomy catheters or nephrostents, often with an attached trocar that can be advanced in a retrograde fashion out of the selected calyx.

Temporary Nonintubated Diversion

Cutaneous Vesicostomy

Cutaneous vesicostomy continues to command a prominent role in the armamentarium due to its simplicity, effectiveness, and low maintenance requirements.[19,20] Most commonly, it is used for patients with a neuropathic bladder or PUVs, in situations where CIC is unable to provide sufficient drainage to prevent hydronephrosis or infection. It must always be remembered that CIC places a significant burden on the family and caregivers, and therefore vesicostomy can be a tremendous relief to the burden of caring for a medically complex and demanding child. A properly functioning vesicostomy results in excellent bladder drainage, negligible bladder pressures, elimination of hydronephrosis due to bladder outlet obstruction, and decreased vesicoureteral reflux.[9,21–23]

The introduction of CIC in early infancy has limited the role of vesicostomy in some centers, and has provided equivalent long-term results.[24] One concern regarding temporary cutaneous vesicostomy is potential impairment in bladder function due to inadequate cycling of the detrusor during the period of diversion.[25] Jayanthi et al. reported on a large group of patients who underwent cutaneous vesicostomy and eventual bladder closure. They found no significant alteration in eventual bladder capacity or function.[26] These findings were also supported in a series of

patients with PUVs managed with either valve ablation or urinary tract diversion, with no evidence of bladder dysfunction based on urodynamics findings in those who had diversion with vesicostomy.[27]

Two basic techniques have been described for cutaneous vesicostomy in children. The procedure described by Lapides involves creation of extensive skin flaps to allow a tension-free anastomosis of the bladder to the skin, and a very wide stoma that is less prone to stenosis.[28] This procedure was initially intended as a semipermanent form of vesicostomy in the adult patient, where the bladder position is deeper in the bony pelvis. Because of the complexity of both creating and taking down the Lapides vesicostomy, there is limited application for the majority of pediatric patients. The more popular technique for vesicostomy in children was described by Blocksom and modified by Duckett, as outlined in Figure 58.3.[9,29] Key technical points are adequate mobilization of the bladder dome for a tension-free anastomosis to the fascia and skin, use of the dome of the bladder to create the stoma, and creating an adequate-caliber stoma (at least 22 Fr) that is flush with the skin.[9,30]

Common problems following vesicostomy are listed in Table 58.2. The majority of complications that lead to stomal revision are secondary to either technical errors of stomal placement inferior to the dome of the bladder, inadequate stomal diameter, or primary bladder pathology. The extremely thick-walled bladder is much more difficult to mobilize, and eversion of even a very wide segment of bladder may not allow an adequate-caliber stoma. A stoma located too cranially can result in the inability to contain the urine in a single diaper (Figure 58.4). This can be very frustrating for the caregiver, but can be managed with a horizontally placed pad or diaper within the normal one.

Bladder prolapse through the vesicostomy stoma is usually due to placement of the stoma too inferior, allowing the posterior bladder wall to evert through the stoma. Acute prolapse can usually be managed with manual decompression and bladder drainage with a catheter through the vesicostomy until the edema subsides. On rare occasions, the prolapsed bladder will incarcerate due to vesicular congestion. This requires emergency reduction under anesthesia. Revision of the vesicostomy by moving the stoma to a more superior position in the dome of the bladder will prevent recurrence.

Stomal stenosis will result in incomplete drainage of the bladder and often present with either UTI or hydronephrosis. Stenosis is thought to occur secondary to excess tension on the skin anastomosis or too small of a fascial opening, and is more frequent in patients with very thick-walled bladder or with prune belly syndrome.[9,30] Simple revision with creation of a wider-caliber stoma or use of a small V-shaped skin flap to disrupt the circumferential stomal scar tissue will usually correct the problem and prevent recurrence.

Cutaneous Ureterostomy

The indications and need for temporary and permanent urinary diversion with cutaneous ureterostomy or pyelostomy have been significantly reduced over the past several decades. Advances in percutaneous and endoscopic techniques have contributed to the trend away from cutaneous upper tract diversion. In addition, we have a better understanding of the pathophysiology and natural history of the dilated ureter in childhood. This has led to observation with radiographic surveillance instead of early surgical intervention in many circumstances.[31] However, despite the majority of asymptomatic, antenatally detected megaureters, the occasional patient will develop febrile UTIs, hypertension, or failure to thrive.[32]

For the ill neonate with an obstructed or refluxing megaureter, a temporary ureterostomy results in excellent urinary drainage, and rapid clinical improvement of the patient.[32,33] This allows for appropriate delay until the child is better able to tolerate a formal reconstruction, as outcomes from a tapered ureteric reimplant have been shown to be better once the child is greater than 1 year of age.[229] Over several months, there is a significant decrease in ureteric caliber, and therefore a simpler ureteric reimplantation. When there is a question of recoverable function, an interval of diversion may help one to decide between reconstruction and nephrectomy.[34]

A distal-end ureterostomy is useful in children with massively dilated ureters secondary to distal obstruction or vesicoureteral reflux that are not candidates for immediate reconstruction.[32,33] The surgical approach is usually through a low transverse muscle splitting incision that allows access to the retroperitoneum. The Pfannenstiel is a logical choice, as it may be required for future reconstruction. The ureter is carefully mobilized to the level of the bladder hiatus and transected, taking care to preserve the periadventitial and retroperitoneal blood supply. The ureteral stoma can be brought out either in the lateral margin of the incision or in the midline. Large-caliber (10 or 12 Fr) straight catheters are left for 3 days postoperatively to minimize the risk of obstruction from edema. A properly located stoma will be contained in the infant's diaper, and therefore is extremely easy to care for (Figure 58.5). A V-shaped skin flap can be used to prevent stomal stenosis, but this occurs infrequently with a dilated ureter.[35] Prophylactic antibiotics are often used postoperatively, but like the vesicostomy, colonization with bacteria is expected, but adequate drainage should mitigate the risk of a symptomatic infection.

In the case of a duplicated system, with an obstructed upper-pole moiety, the dilated ureter can be brought out in isolation, but great care is required to preserve the blood supply to the normal lower-pole ureter and to prevent its kinking.

The benefits of a more proximal ureteric diversion include the ability to perform renal biopsy for determining renal prognosis, the ability to accurately monitor the function of each kidney individually, and allowing a period of observation to decide on eventual reconstruction. Controversy still exists with respect to the benefit of a high ureterostomy in patients with PUVs who have persistent severe hydronephrosis and azotemia despite ablation of the valve or diversion with vesicostomy. Earlier studies suggested that proximal ureteral diversion would result in relief of functional obstruction at the ureterovesical junction and improve eventual glomerular filtration rate and somatic growth potential.[36,37] More recent studies, however, have challenged this concept, demonstrating no difference in eventual renal outcome between children who

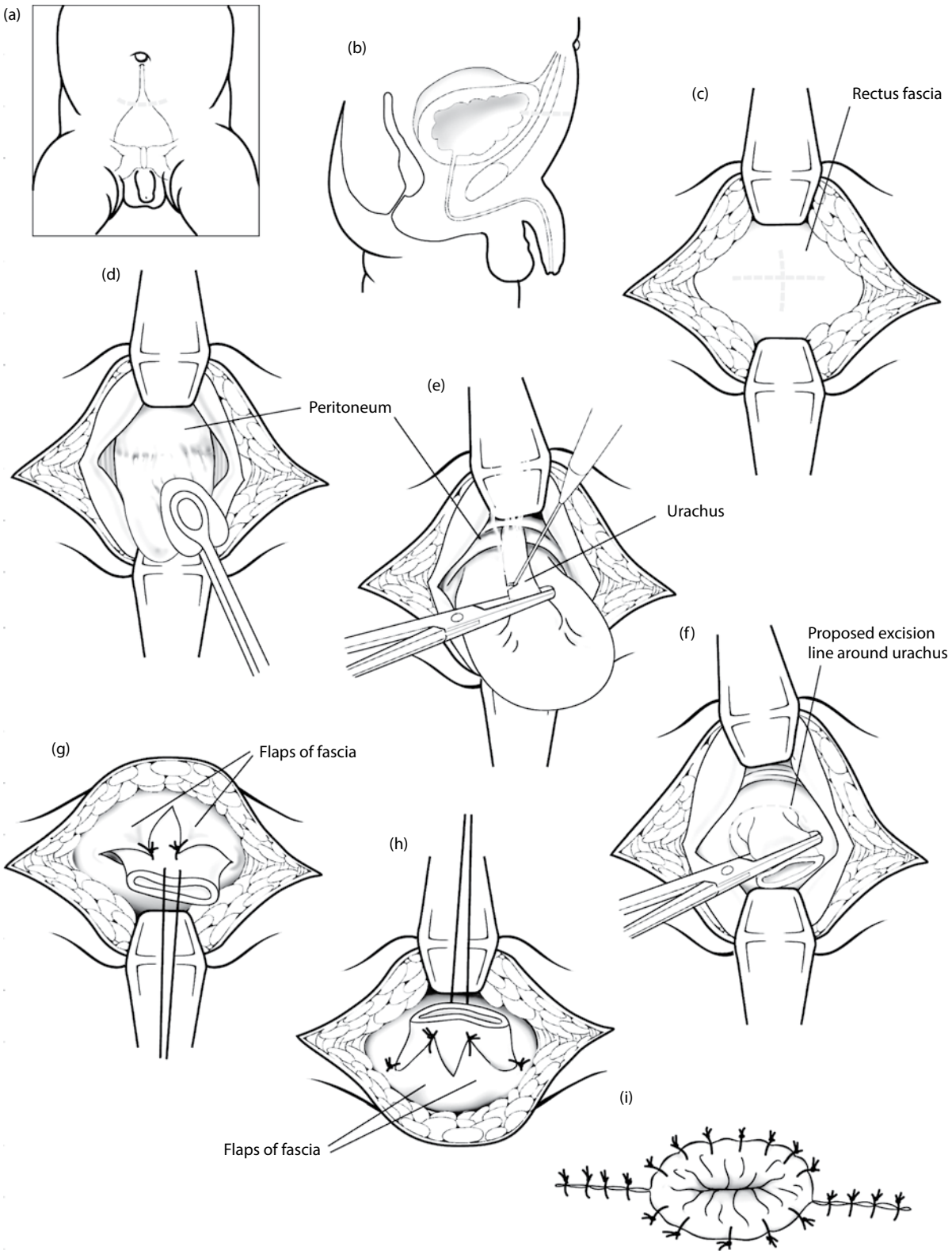

FIGURE 58.3 Technical points for Blocksom vesicostomy. (a, b) A small transverse skin incision is made midway between the pubis and umbilicus. (c) The rectus fascia is opened vertically and horizontally, and the muscle is retracted laterally. (d) Stay sutures are placed in the bladder, and the peritoneum is bluntly mobilized superiorly, exposing the bladder dome. (e) The urachus is identified and divided. The urachal segment is mobilized until it reaches the skin without tension. (f) The urachus is excised, ensuring an adequate-caliber opening into the bladder (22–24 Fr). (g) The detrusor is circumferentially secured to the rectus fascia. (h) The lateral edges of the fascia are closed, allowing easy passage of a 22–24 Fr sound. (i) The bladder mucosa and detrusor are secured to the skin, and the lateral skin edges are closed in layers.

TABLE 58.2 Complications of cutaneous vesicostomy

Complication	Frequency (%)
Stomal prolapse	9–17
Stomal stenosis	3–12
Peristomal dermatitis	3–14
Stone formation	3–7
Parastomal hernia	3–4

Source: Skoog S. Pediatric vesical diversion. In Graham S, ed., *Glenn's Urologic Surgery*. Philadelphia: Lippencort-Raven, 1998, 872–8.

FIGURE 58.4 Photograph of a vesicostomy stoma located too cranially. The family was unable to manage the urinary drainage with standard diapers.

FIGURE 58.5 Photograph of an infant with bilateral ureterostomies performed in the neonatal period for left grade 5 reflux, right ureterovesical junction obstruction, sepsis, and renal insufficiency. The stomas are easily placed into the diaper, allowing for minimal maintenance, and the same incision is used for subsequent reimplant, minimizing scarring.

are managed with primary valve ablation and patients with an upper tract diversion.[38,39] Those who oppose routine proximal diversion think that the improved renal function following diversion is attributable to normal transitional nephrology that occurs with or without diversion.[39,40] In a study of 26 patients managed with bilateral high diversion for PUVs, Tietjen et al. reported renal dysplasia on biopsy in 85% and true ureterovesical junction obstruction based on Whitaker studies in only 4%.[40]

Potential problems of ureterostomy include ureteral kinking, stomal stenosis, the need for a more complex reconstructive procedure at a later date, impaired ureteral vasculature, and difficulty in covering the stoma with an appliance as the child grows.

The techniques for proximal diversion have not changed significantly for several decades. There is still debate over the preferred technique,[34] i.e., whether a pyelostomy, loop, or Y-ureterostomy should be utilized. The Y-ureterostomy, as described by Sober, allows for urine flow to the bladder, preserving some degree of bladder cycling.[41] This avoids the potential later problem of carrying out a complex lower tract reconstructive procedure in a small, defunctionalized bladder. Regardless of the technique used, adhering to three basic operative principles is critical for a successful outcome:[42] (1) during mobilization, the ureter should be manipulated to the least degree possible; (2) ureteral mobilization should be minimized to preserve maximal blood supply, yet be adequate to allow a tension-free skin anastomosis; and (3) kinking of the ureter or compression by the abdominal wall at the stomal site must be avoided.

Techniques for high ureterostomy are illustrated in Figure 58.6. All these procedures can be accomplished through a subcostal or flank incision, which allows mobilization of the ureter proximally to the renal pelvis and creation of a tension-free anastomosis to the skin. Loop ureterostomy is preferred by some surgeons because of the simplicity of the procedure. Closure of the ureterostomy and lower urinary reconstruction are often staged but can be performed simultaneously if there is careful attention to the periureteral vasculature.

Cutaneous Pyelostomy

Cutaneous pyelostomy has limited applications, but it can be an effective option for upper tract diversion. Best suited for patients with a dilated extrarenal pelvis that can easily reach the skin, the advantages of this procedure include

1. Minimal disturbance of ureteral blood supply during both formation and closure of the stoma
2. Direct urine drainage and avoidance of urinary stasis in the dilated distal ureter

The pelvis is easily accessed via a flank incision or a dorsal lumbotomy,[37] mobilized and exteriorized superior to the ureteropelvic junction, with great care to avoid angulation, obstruction, and stenosis (Figure 58.7).

Incontinent Urinary Diversions

With the advances made in medical prevention and an increased acceptance and desire for continent bladder reconstruction, the usage of permanent, noncontinent urinary diversion in children has significantly decreased. However, just as the vesicostomy provides for the simplest and most effective means of urinary drainage in the infant, its use in the older child and adolescent is hampered by high rates of stomal stenosis and desire to avoid diapers. An incontinent urinary diversion must always be considered in the complex patient who does not have the

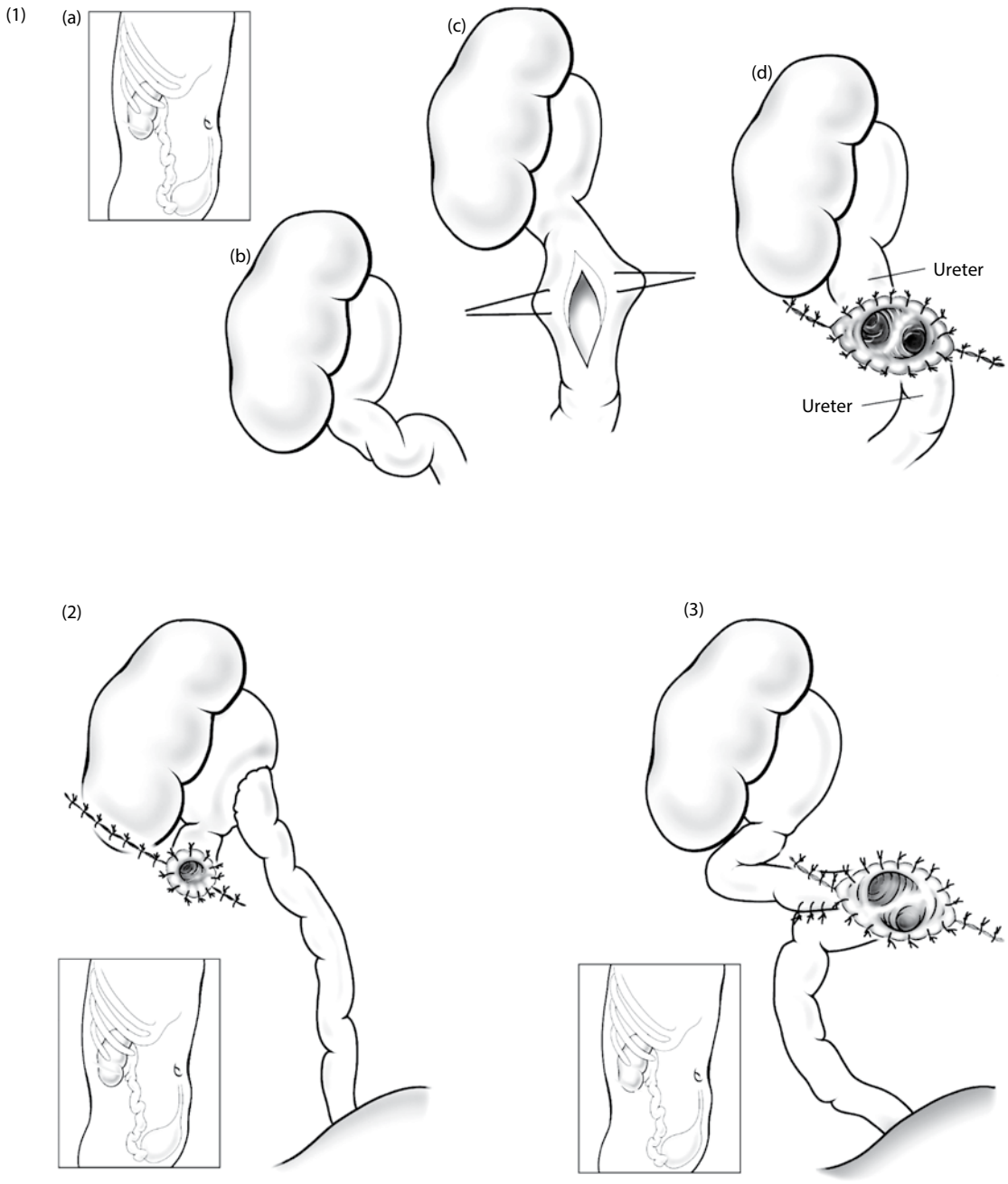

FIGURE 58.6 Various options for high cutaneous ureterostomy: (1) loop ureterostomy; (2) Sober ureterostomy; and (3) ring ureterostomy. Care is taken with each technique to preserve the medial blood supply and create a tensionfree skin anastomosis.

desire, resources, or physical or mental resources required for the significant effort that is mandated from a continent reconstruction.

These techniques can offer a simple, low-maintenance, and effective means of urinary drainage, although there are some long-term concerns about a higher degree of renal deterioration.[43–48] Patients with limited ability to care for themselves due to physical or mental disability and children with malignancies who have undergone extensive pelvic or abdominal radiation or who have limited life expectancy may be excellent candidates for an incontinent urinary diversion. As opposed to recommendations in the adult population,[49,50] renal failure in children is not an absolute indication for conduit diversion, as most children will be candidates for renal transplantation and will have a better eventual outcome with primary bladder reconstruction.[51,52]

Urinary Conduit

Any segment of small or large intestine can be used to create a urinary conduit; however, the ileum and colon are most frequently selected. Some surgeons prefer using colon conduits in children as the tenia facilitates a nonrefluxing anastomosis, which may ameliorate long-term renal deterioration.[44,47]

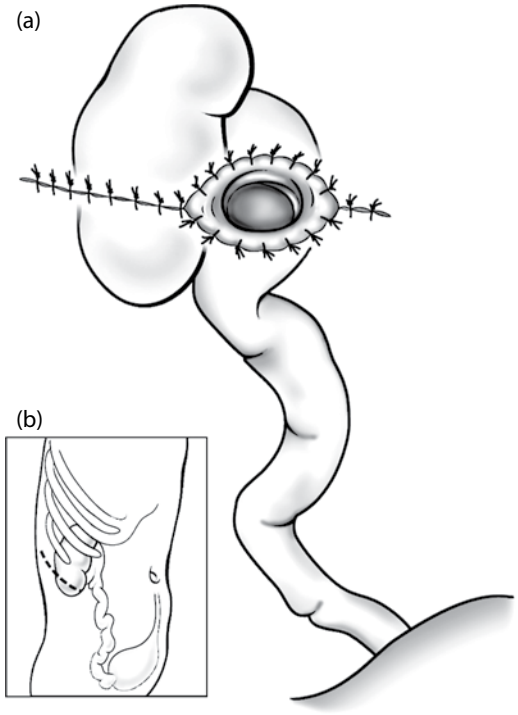

FIGURE 58.7 Cutaneous pyelostomy. (a) The renal pelvis is approached through a subcostal, posterior flank or dorsal lumbotomy incision. The kidney and dilated renal pelvis are mobilized until the renal pelvis can reach the skin without tension. (b) The renal pelvis is opened widely and secured to the skin with interrupted, absorbable sutures.

The ability to incorporate the colon segment into a continent reservoir at a later date without the need to revise the ureteral anastomosis is also advantageous.[53] Jejunal conduits carry an unacceptably high risk of severe metabolic problems and are not recommended. The primary electrolyte problem with incorporating jejunum into the urinary tract is hypochloremic, hyponatremic, and hyperkalemic metabolic acidosis.[53]

The important technical aspects of creating a conduit are similar whether using the ileum or colon. This starts with an appropriate mechanical and antibiotic bowel preparation, which may need to be altered based on specific patient needs in the pediatric population. Although several reports exist promoting intestinoplasty without a bowel preparation, we feel that the risk of ventriculoperitoneal (VP) shunt contamination warrants the extra caution. The standard pediatric bowel preparation involves admission to the hospital on the day before surgery for intravenous antibiotics to sterilize the urinary tract and whole gut lavage with a polyethylene glycol solution (GoLYTELY) via nasogastric tube until stools are clear. Another key aspect of the preoperative preparation is identifying an appropriate location for the stoma, which is most effectively done with the input of an enterostomal therapist with the child awake before surgery. Several locations should be identified that allow optimal fitting of the appliance with the patient in the sitting, standing, or supine position. This is most critical for the wheelchair-bound patient who may have significant abdominal girth.

TABLE 58.3 Complications of ileal and colon conduits

	Frequency (%)	
Early complications	Ileal	Colon
	Conduit	Conduit
Bowel obstruction	10	4
Urinary leak	3	5
Pyelonephritis	12	13
Late complications		
Stomal stenosis and parastomal hernia	24	20
Renal deterioration	18	15
Metabolic acidosis	16	5
Ureteroenteric stricture	8	9
Renal calculi	7	5

Source: McDougal WS. In Walsh P et al., eds., *Campbell's Urology*, Philadelphia: WB Saunders, 1998, 3121–61.

Although the incidence of postoperative complications may differ slightly for colon or ileal conduits, the types of associated problems are very similar and can be divided into early or late complications (Table 58.3). Both ureteroenteric and stomal complications are generally related to surgical technique, representing the most common problems leading to reoperation. The general principles of minimal handling of the ureter, maintaining maximal adventitial blood supply, minimizing mobilization, preventing angulation of the ureter, and securing a mucosa-to-mucosa watertight anastomosis with fine absorbable sutures will decrease the potential for postoperative problems. The use of ureteral stents has been shown to significantly decrease anastomotic leaks.[54] Suspected ureteral leaks should be promptly investigated and, if present, treated by a percutaneous nephrostomy tube drainage and antegrade stent placement.

Ureteral strictures can been seen early after surgery, or may take several years to form,[55] reinforcing the need for long-term periodic radiographic surveillance. Treatment of strictures at the ureteroenteric anastomosis can be initially attempted with endourologic techniques. Regardless of the technique used (balloon dilation alone vs. incision and dilation), approximately 50% will eventually require open revision.[55,56]

Stomal problems may vary from a minor nuisance (bleeding and dermatitis) to more life-threatening complications, such as stomal obstruction with UTI

- Bleeding
- Bowel necrosis
- Dermatitis
- Parastomal hernia
- Stomal prolapse
- Stomal stenosis
- Stomal retraction
- Loop obstruction (early or late)

Stomal complications rates are reported to occur in 15%–80%. Problems with local skin irritation can be minimized by creating an everted nipple or loop stoma, so

that the appliance can be fit snuggly to the adjacent skin. Stomal stenosis and parastomal hernia are the most common problems with conduit diversion that require surgical revision. The risk of these complications can be minimized by bringing the bowel through an adequately sized fascial defect without angulation, securing the conduit to the fascia in four quadrants, and creating a nipple stoma.[57] It was initially thought that colon conduits had a lower incidence of stomal stenosis than ileal conduits, but this has not been supported in more contemporary series.[58] Skin and peristomal complications are best dealt with by an enterostomal therapist, preferably with pediatric expertise.

If the bladder is left in situ, the lack of drainage and urine may result in pyocystis. Therefore, some authors recommend cystectomy if a conduit diversion is chosen for benign disease.

Tumor within a conduit has been reported using both ileal and colon segments.[59] Although the risk for malignancy is unknown, it should be significantly lower than for ureterosigmoidostomy where urine and stool are mixed.

Technique for Ileal Conduit

The abdomen is opened through a midline incision, and the ureters are identified and mobilized at the level of the iliac bifurcation. The left ureter is brought across the midline in a retroperitoneal tunnel, taking care to avoid angulation. A 10–15 cm segment of ileum is selected that has an adequate vascular arcade, and the mesentery to this segment is isolated. The mesentery of the distal end of the segment is mobilized off the bowel to allow this end to be brought up to the skin as the stoma. *The last 15 cm of distal ileum should be avoided, as this segment of ileum is important for iron and vitamin B_{12} absorption*. The bowel segment is harvested and bowel continuity is restored using either a side-to-side stapled or end-to-end hand-sewn anastomosis. The mesenteric defect is closed with permanent suture. The proximal end of the conduit is closed in two layers (after removing the staples if a stapling device was used to harvest the segment) and secured to the sacral promontory. Ureteroileal anastomoses are carried out using either the Bricker[60] or Wallace[61] technique (Figure 58.8a and b), the proximal end of the loop is brought out at the predetermined site for the stoma, and an everting nipple or loop stoma is created (Figure 58.9).

Technique for Colon Conduit

The colon conduit is constructed in a fashion similar to that for the ileal conduit, with the exception of the ureteral anastomosis, which is usually created in a nonrefluxing manner using the tenia (Leadbetter technique) (Figure 58.10). Alternatively, a submucosal tunnel may be created (Goodwin technique).[50] Injecting saline or dilute epinephrine under the mucosa will minimize bleeding and aid in the dissection. Because of the added risk of ureteral obstruction within the submucosal tunnel, stenting the ureteral anastomosis is recommended.

Most commonly, a sigmoid segment will be used to create the conduit (Figure 58.11), but in children with a history of pelvic radiation or inadequate ureteral length, the transverse colon should be used.

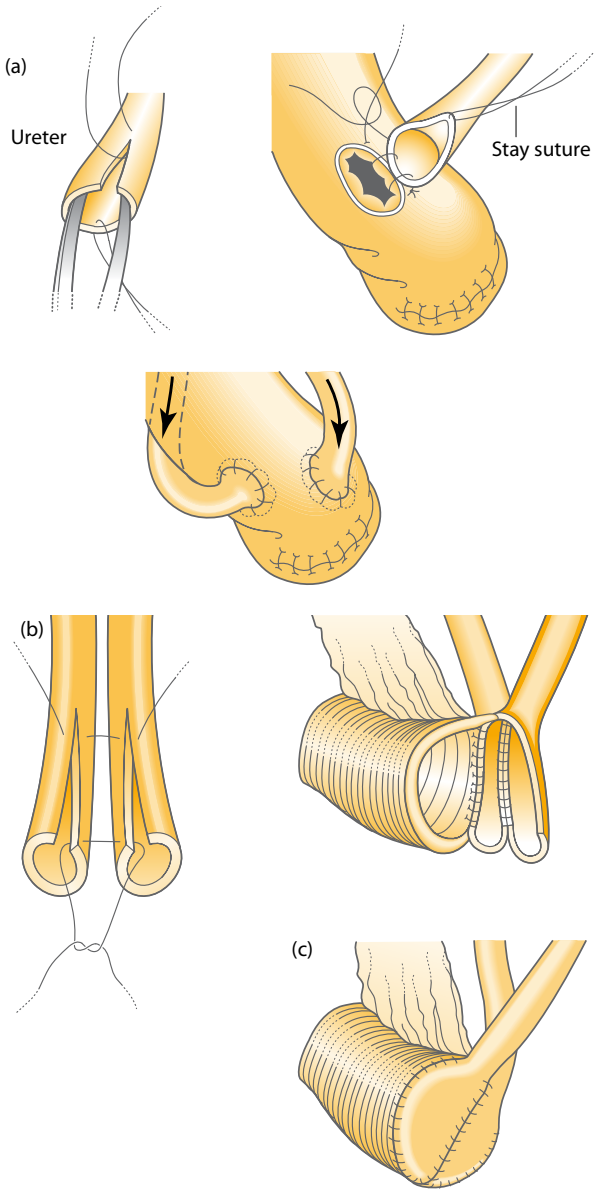

FIGURE 58.8 (a) The Bricker technique for ureterointestinal anastomosis. The ureter is spatulated, and following excision of a small ellipse of intestine, the anastomosis is secured with fine interrupted absorbable sutures. The external stent is placed across the anastomosis and brought out through the stoma. Both ureters are secured using an end-to-side anastomosis. (b) The Wallace procedure for ureteroileal anastomosis. The ureters are spatulated and joined at their medial borders using running or interrupted absorbable sutures. (c) The lateral edges of both ureters are then secured to the conduit in an end-toend anastomosis.

Ileocecal Conduit

By using the nonrefluxing properties of the ileocecal valve, the ileocecal conduit provides an alternative to the tunneled ureteral reimplantation used to achieve a nonrefluxing ureteral anastomosis with other colon conduits. The ileocecal conduit can later be incorporated into a ureterosigmoidostomy with reduced risk of cancer, as the ileocecal valve will prevent the direct contact of feces and urine at the site of the ureteral anastomosis. The greatest

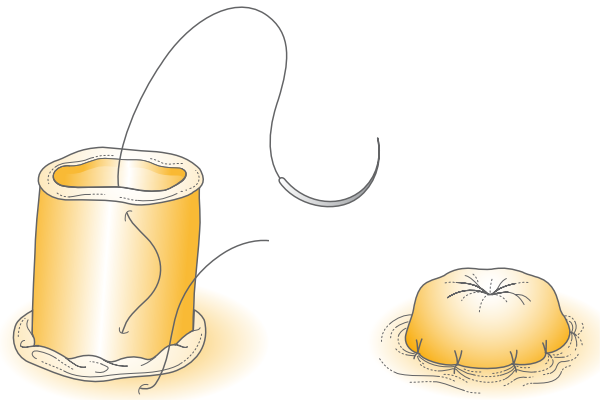

FIGURE 58.9 An everted stomal nipple is optimal for creating a snuggly fitting appliance. This is created by placing sutures between the skin/subcutaneous tissue, lateral bowel serosa, and distal edge of the stoma.

concern in using this segment for urinary diversion is the theoretical risk of diarrhea and fecal incontinence in the myelomeningocele patient who may depend on the intact ileocecal valve to prevent rapid transit of liquid stool into the colon. The technique involves isolating a portion of the right colon and distal ileum (Figure 58.11). The ileocecal valve is reinforced with permanent plication sutures that intussuscept the valve into the cecum.[62] The ureters are reimplanted into the proximal portion of the ileum using either the Bricker or Wallace technique.

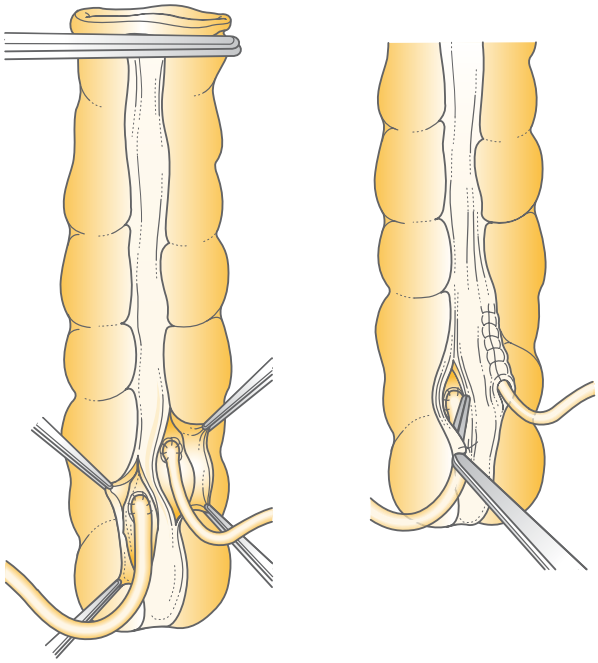

FIGURE 58.10 The non-refluxing ureterocolonic anastomosis described by Leadbetter. A submucosal tunnel is created by incising the tenia to create a submucosal trough, the ureter is anastomosed to the colonic mucosa, and the muscularis loosely closed over the ureter with absorbable suture.

Ileovesicostomy

Although animal studies and the first reports occurred more than 50 years ago, McGuire popularized the ileovesicostomy in patients with spinal cord injury.[2] The obvious advantages to the patient are a low-pressure reservoir and simple maintenance. By keeping the bladder in situ, the patient has minimal risk of pyocystis and avoids the potential complications of the cystestomy and ureterointestinal asatomosis. Long-term outcomes have been good, although revision surgery and infections are common.

Continent Urinary Diversion

The incredible progress in medical care of the complex pediatric patient has elevated expectations to beyond simple survival. Patients and families have promoted and increased interest in quality of life and integration into mainstream society. For the pediatric urologist, this has heralded the advent of continent urinary reconstruction, whereby a multitude of surgical techniques have evolved to provide the potential for urinary continence. Because the vast majority of our patients' pathophysiology arises from nonmalignant causes, their bladders may be left in situ, and the majority of reconstructions involve bladder augmentation. This is not addressed in this chapter, and the focus remains on urinary diversion.

A true CUR implies that a reservoir to store urine has been constructed entirely from the gastrointestinal tract, with no detrusor present, and is emptied by CIC, usually via the abdominal wall. Gilcrest and Merricks created the first modern-day reservoir by making a cecal bladder with continence based on the ileocecal valve, with the ileal "urethra" brought to the abdominal wall.[63] Gilcrest et al. reported good success with this, but others had difficulty in duplicating their results. One of the major impediments to widespread adoption was that intermittent catheterization was not well accepted.[64,65] Gilcrest continued to use this method and was able to achieve continence in 37 of 40 patients.[66,67]

The orthotopic *neobladder* is constructed from gastrointestinal segments attached directly to the native urethra, allowing the patient to spontaneously void. Neobladders are now commonplace in adults who require cystectomy for cancer, but are rarely used in the pediatric population. In children, the native bladder is often left in situ, and instead of replacement, it is augmented with a gastrointestinal segment. This is commonly referred to as a bladder augmentation, or an ileocystoplasty. This also requires drainage via CIC, through either the urethra or a catheterizable abdominal wall channel. For the purposes of this chapter, we do not consider orthotopic neobladders or enterocystoplasty, and focus on CURs.

Lapides's introduction of CIC in the 1970s was critical in the implementation of the reconstructive techniques we know today.[68] With acceptance of CIC, volitional voiding was no longer required, and therefore the reconstruction only needed to recapitulate the storage function of the bladder. In addition, accurate urodynamic evaluation in children allowed for improved renal outcomes and improved patient selection.[69] Reliable pediatric anesthesia

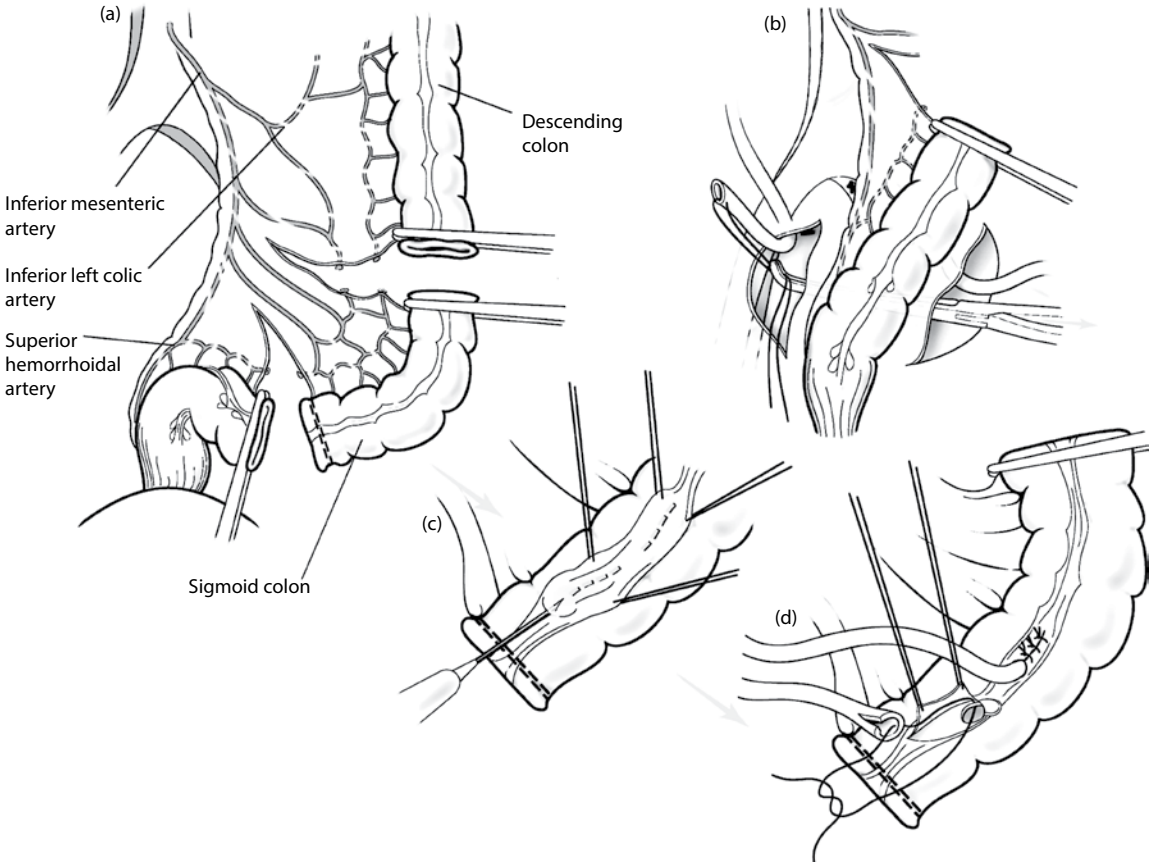

FIGURE 58.11 Surgical technique for creation of a sigmoid colon conduit. (a) A segment of colon is isolated, maintaining a wide mesenteric pedicle. (b) The ureters are mobilized through posterior incisions in the peritoneum and transected. The right ureter is brought across the midline in a retroperitoneal tunnel. (c) The tenia is incised to create a tunnel. (d) The ureters are anastomosed, as illustrated in Figure 58.10.

now permitted long reconstructive cases to be safely performed. Finally, Hendren's demonstration that the previously diverted urinary tract could be refunctionalized (undiversion) also spurred the decline of incontinent diversion in children.[70,71]

Kock's continent urinary ileal reservoir was the first widely used CUR, which was adapted from his continent ileostomy.[72] The Kock pouch was refined and further popularized by Skinner's team.[73–75] Over the past 25 years, there have been more than 40 variations of CURs described. Gastrointestinal CURs have been used in the adult population primarily as a means of diversion following cystectomy. In these adult patients, the urinary and gastrointestinal tracts are usually anatomically and neurologically normal, allowing the surgeon to use one of the many named procedures, such as the Kock pouch, Indiana pouch, or Mainz pouch. However, the majority of children undergoing true CURs, such as those with classic exstrophy or myelomeningocele, have significant anatomic and/or neurologic abnormalities. Some have a combination of both abnormalities, such as the cloacal exstrophy patient, who is more susceptible to short gut syndrome.[76] In these situations, creation of a standard named CUR may not be possible. These anatomic and neurologic abnormalities do not prevent continent urinary diversion in children, but they do require the surgeon to have a fertile imagination and depth of knowledge of all options available, as well as a good understanding of the concepts necessary to provide a reliable reservoir.

Patient Selection and Preoperative Evaluation

It is our belief that the urinary tract should remain intact whenever possible. In this regard, all efforts should be made to exhaust medical management prior to electing surgical options. Reconstruction is generally performed for one of two reasons: to protect the upper urinary tract or to achieve urinary continence. In the majority of children with lower urinary dysfunction, these two goals can be achieved with CIC and/or pharmacologic management. In our experience with the neuropathic population, approximately 70% can be managed nonsurgically. If this fails, then we would not hesitate to reconstruct the lower urinary tract, but this again usually involves reconstructing the native bladder by enterocystoplasty and bladder neck reconstruction rather than CUR.

The most common contemporary reason to construct a true CUR (without any native bladder being used) in a child, like in the adult population, is after a genitourinary malignancy. Although bladder-sparing protocols are being popularized, the severe doses of radiation and chemotherapy can leave the patient with an unusable or unsafe

bladder. Excellent long-term results have been reported in the pediatric population.[77,78]

For any continent reconstruction, the child must have adequate upper extremity function to catheterize reliably and the mental capacity to do so. The patient and/or family must be motivated and reliable. Both must understand that a lifelong commitment to CIC is required, and failure to catheterize reliably may result in urinary infection, stone formation, reservoir perforation, or renal deterioration, even in the face of a technically perfect operation.

Preoperatively, the overall renal function should be determined by measuring serum creatinine and electrolytes. It cannot be overstated that the very high doses of chemotherapy used in pediatric malignancies can be significantly nephrotoxic. Benson and Olsson suggest that no patient should undergo reservoir creation if creatinine clearance is <60 mL/min.[79] With the incorporation of ileum or colon into the urinary tract, chloride and ammonium are absorbed and sodium bicarbonate is excreted, which may result in a hyperchloremic metabolic acidosis (Figure 58.10). This was first noticed by Ferris and Odel in patients with ureterosigmoidostomy.[80] Children with normal renal function generally tolerate this well, but in those with renal insufficiency, a severe metabolic acidosis may occur.[80–82] Mitchell and Piser noted that the chloride level increased and bicarbonate level decreased in every patient following enterocystoplasty at their institution.[83] Rink et al. later reviewed 231 patients and found 16% to have a serum chloride level above the normal range.[84] Those patients with severe elevations all had colonic segments in their urinary tract. Others have reported similar findings following CURs.[85–89] These changes would be expected to be more severe in CURs where the entire storage surface area is enteric, rather than with augmentation of the native bladder. Nurse and Mundy demonstrated that following enterocystoplasty, the blood gas values may be abnormal even with normal serum chloride levels.[90] There has been concern regarding poor linear growth from the use of bony buffers in response to chronic acidosis.[90–94] Others have found no significant difference in growth or bone density.[95,96] Regardless, both groups would agree that if acidosis exists following CUR, bicarbonate therapy should be started.

Many children undergoing creation of a CUR have renal tubular dysfunction from primary urinary obstruction, resulting in a severe urine-concentrating defect. The end result may be the excretion of very large volumes of urine. Therefore, a 24-hour urine for volume should always be checked preoperatively. The reservoir must be made large enough to handle the patient's urine output adequately at low pressures to allow emptying no more frequently than every 4 hours. A technically perfect CUR would be inadequate if it required catheterization every 2 hours plus awakening at night to catheterize. Graphs and guidelines have been developed to predict the length of a bowel segment needed to achieve a certain volume.[97] However, these graphs may prove cumbersome and are not routinely used.[98] Even if renal and bowel function are normal, it is better to err on making the reservoir too large than too small. However, unlike the fibrotic or diseased bladder they are replacing, CURs have shown the ability to increase in capacity. Anticholinergics may also be used to decrease any residual contractility and improve compliance.

Liver function testing should also be carried out, as suggested by McDougal.[50] Hyperammonemia can occur in patients with large or small intestine incorporated into the urinary tract when hepatic dysfunction is present, as these segments absorb ammonium.

In all children, the urinary tract must be imaged preoperatively. A combination of ultrasonography and radionuclide scanning will adequately assess structure and function. Ureters, which have undergone prior reimplantation, may be hydronephrotic due to fibrosis and aperistalsis, as opposed to increased storage pressures. Therefore, even though the bladder is not being used, videourodynamics can be very helpful, especially after radiotherapy to the pelvis.

If the CUR is being performed after removal of the bladder or prostate after a malignancy, all efforts should be made to ensure that chemotherapy is finished and the patient declared free of residual disease.

Stomal location should also be determined before the operative procedure. All efforts should be made to place the stoma on the abdomen corresponding to the dominant hand of the patient. While this is less important for continent diversion than conduit diversion, it is still important to be certain the child will be able to pass the catheter easily. Skin folds and areas of abdominal wall scarring should be avoided. It is best if the patient can visualize the stoma. The stoma may be placed in an orthotopic location to allow catheterization of a normal urethral meatus, but in most patients, this is not warranted. In a study by Horowitz et al., patients who had the opportunity to catheterize either their native urethra or an abdominal wall stoma overwhelmingly preferred the latter.[99]

Finally, latex allergy precautions must be observed in all patients with spinal dysraphism.

Principles of Continent Urinary Diversion

The ideal reservoir (1) provides the high-capacity, low-pressure reservoir that the kidneys require to minimize pressure on the upper urinary tract, (2) avoids reservoir-ureteral reflux and ureteral obstruction, (3) allows for simple and effective emptying, (4) is continent, and (5) has minimal short- and long-term complications.

Creation of a Compliant Reservoir

Fashioning the ideal reservoir of the CUR will depend on the underlying diagnosis and the patient's anatomy. Virtually all gastrointestinal segments have been used to create CURs, and therefore it is important to know the pros and cons of the gastrointestinal segments available and the length and configuration of the bowel segment chosen. The promise of a tissue-engineered bladder substitute is extremely exciting, and although substantial progress has been made, the promise of human application will still require further innovation and time.

The native bowel is capable of significant peristalsis, and if left unmodified, very high reservoir pressures may be generated by the intestinal contractile activity. Multiple studies have demonstrated bowel segments capable of

pressures of 60–100 cmH_2O.[100–103] These high pressures can result in urinary leakage and upper urinary tract deterioration, and may even contribute to perforation.[104] Since McGuire et al.'s landmark paper, it is now well accepted that intravesical (intrareservoir) pressures must be maintained well below 40 cmH_2O. More recent data with laboratory research suggest that intravesical pressures far less than 40 cmH_2O may have a deleterious effect on the bladder.[105–107]

Therefore, regardless of the gastrointestinal segment used, it is imperative that the segment is detubularized and reconfigured into a sphere (Figure 58.12).[108,109] Detubularization will dampen the contractile activity of the segment, and thereby increases tissue compliance. However, the surgeon must understand that contractile activity is not totally abolished by detubularization. In fact, Lytton and Green found contractions up to 60–110 cmH_2O in patients reconstructed with detubularized right colon,[110] and Sidi et al. noted average peak pressures of 41 cmH_2O following cup-patch sigmoid cystoplasties.[111]

Although the ileum is often considered to have much lower peristaltic activity, detubularization is still required to minimize pressures in the ileum, as recorded pressures of 81 cmH_2O were seen in native, tubularized ileal reservoir versus 28 cmH_2O in the detubularized ileal reservoir. Clinically significant contractions (>40 cmH_2O at volumes <200 mL) were observed in 10% of the right colon and none of the ileal segments. Ileal segments were thought to be urodynamically superior, especially at large volumes.[112]

The reservoir must also have sufficient capacity to allow storage of at least 4 hours of urine production. This volume must consider the patients with high outputs secondary to renal tubular concentrating defects (i.e., PUVs). Reconfiguring the segment from its native cylinder to a sphere has the advantages of increasing the capacity from the same amount of tissue. Furthermore, from LaPlace's law ($t = Pr$, where t = wall tension, P = pressure, and r = radius), the larger the radius (r), the greater the wall tension (t), resulting in enlargement over time.

If upper tract deterioration or urinary leakage occurs, urodynamics must be repeated to ensure reservoir pressures are satisfactory. In the author's augmentation cystoplasty population, a second segment of bowel had to be added in 19 of 323 patients owing to persistently elevated pressure in the initial bowel segment.[113] Twelve of 87 undergoing colocystoplasty (13.8%), 4 of 30 undergoing gastrocystoplasty (13.3%), and only 2 of 145 ileocystoplasties (1.4%) required a secondary augmentation bowel segment.[113] The authors agree with Goldwasser and Webster that ileum is the least contractile intestinal segment, with cecum intermediate and sigmoid and stomach being the most contractile.[113,114]

Choice of Bowel Segment

While some of the metabolic and contractile properties of the gastrointestinal tract have been discussed above, there remain several advantages and disadvantages of each segment (Table 58.4). Several studies have reported on experience with the various gastrointestinal segments used in reconstructing the lower urinary tract.[53,98,104,115] The majority of data in children come from augmentation cystoplasty rather than complete reservoir construction.

Ileum, as noted previously, when reconfigured, will provide the most compliant, least contractile segment. Mucus production, while greater than with the stomach, is less than with the sigmoid or cecum and tends to decrease with time.[116] Hyperchloremic acidosis occurs with small and large bowel but seems to be less significant with the ileum.

Except in instances of short gut syndrome, as in cloacal exstrophy, there is generally an abundance of ileum available for reservoir construction and for the creation of catheterizable channels. If short ureters are present, a "tail" of ileum extending from the pouch can be used to bridge the gap. However, at times the mesentery is short, making an anastomosis to an orthotopic catheterization site difficult.

The ileum is responsible for vitamin B_{12} absorption, which occurs in the terminal portion. If possible, the distal 15 cm of ileum should be preserved. Resection of

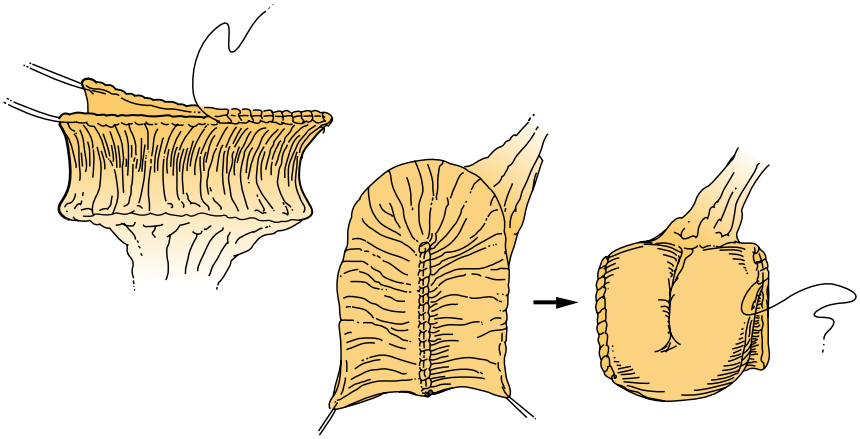

FIGURE 58.12 The bowel must be detubularized (upper left) into more of a flat plate and reconfigured into a sphere (bottom right) to minimize peristalsis and maximize the ratio of surface area to volume. (From Indiana University, Indianapolis, Indiana. With permission.)

TABLE 58.4 Advantages and disadvantages of each segment

Segment	Advantages	Disadvantages
Ileum	Most compliant	Diarrhea
	Less mucus	Vitamin B_{12} deficiency
		Short mesentery
		Hyperchloremic acidosis
		Poor muscle backing
Sigmoid	Readily mobilized	Unit contractions
	Easily implanted	Lower compliance
	Good muscle backing	Mucus
		Hyperchloremic acidosis
		Perforation risk
Ileocecal	Valve as antireflux or continence mechanism	Diarrhea
	Good-capacity reservoir	Not always available
	Constant blood supply	Contractile
Stomach	Useful as alternative to intestine for short gut or lower abdominal/pelvic radiation	Hypochloremic alkalosis
	Chloride pump	Rhythmic contractions
	Minimal mucus	Hematuria and dysuria
	Few infections	
	Ease of implantation	
	Good muscle backing	

long segments of ileum have resulted in B_{12} deficiency but may take several years to clinically manifest as a megaloblastic anemia and neuropathy, as B_{12} stores may last for years.[53,117,118] Akerlund et al. noted this problem in patients following Kock pouch construction.[119] Canning et al., however, did not find any patients with a B_{12} deficiency in 26 patients evaluated following bladder augmentation using ileum, but this group was followed for only 3 years.[120] A large cohort of bladder augmentations at Indiana University did not find any clinical manifestations of B_{12} deficiency, although levels in many were low, and the authors recommended supplementation.[121] The Mainz group also looked at vitamins A, B, B_2, B_6, D, and E and folic acid levels, as well as bone density, after their diversions, and all were within normal limits.[122] Vitamin B_{12} levels and bone density were normal in the 51 children but dropped significantly in adults. They recommend checking B_{12} levels after 4 years.[122]

Resection of large segments of ileum has also been found to result in diarrhea and to increase the risk of cholelithiasis.[118,123] Roth et al. reported the occurrence of chronic diarrhea in 11% of patients who had a CUR constructed from ileum.[124] Baker and Gearhart noted that if >100 cm of ileum is resected, steatorrhea and cholelithiasis can develop.[125]

The cecum and ileocecal segments have been the most widely used tissues for CUR construction. The ileocecal segment has a constant, reliable blood supply that allows easy mobilization and placement of the pouch in the pelvic inlet, when necessary. The large cecal size makes for an excellent reservoir, and the ileocecal valve can be used to augment either the continence or antireflux mechanisms. The appendix is also readily available for use as a continent catheterizable channel. This segment is used in several of the most popular reservoirs, i.e., the Indiana pouch, Florida pouch, Mainz pouch, and Penn pouch.

In patients with a spinal dysraphism, the ileocecal valve may be important in maintaining fecal continence. Roth et al. noted that 23% of patients having an ileocecal reservoir had chronic diarrhea.[124] Gonzalez and Cabral reported that a patient required replacement of the ileocecal valve to reverse or correct intractable diarrhea.[126] Furthermore, in cloacal exstrophy patients the colonic segment may have been absent or discarded at the time of previous surgery, and thus not available for use. Cecal incorporation into the urinary tract may lead to hyperchloremic metabolic acidosis, as well as significant mucus production.

The sigmoid colon was historically used a great deal in lower urinary tract reconstruction in children. It is often quite enlarged and redundant in the spinal dysraphism population, allowing it to reach easily any portion of the abdomen or pelvis. Its mucosa can be easily dissected to provide submucosal tunnels for antireflux or continence mechanisms. While it seemingly has a number of advantages, it has the disadvantages of significant contractile activity in spite of detubularization and reconfiguration.[113] It also has the greatest mucus production[116] and highest rates of bacteriuria,[127] and is most likely to result in significant hyperchloremic metabolic acidosis. In the authors' hands, when used to augment the bladder, it has resulted in the highest spontaneous bladder perforation rate.[104] However, this latter problem was not found in other series, where complete detubularization and reconfiguration was performed.[128,129]

The use of the stomach in lower urinary reconstruction in children was popularized with the initial report by Adams et al., which purported several unique advantages.[130] The stomach has excellent muscle backing, facilitating ureteral implantation or tunneled continence channels.[131] The stomach was also thought to be an ideal tissue for those who had undergone pelvic radiation, as it is generally outside the irradiated field. Bladder calculi, secondary to mucus production, have nearly been nonexistent with the use of the stomach.[132–134] Kaefer et al. found that only 2 of 70 patients developed stones with the use of stomach compared with 30 of 137 with stones following the use of other enteric segments. Perhaps most importantly, the stomach differs metabolically from the other intestinal segments.[135] Gastric mucosa has no absorptive properties, so the risk of metabolic acidosis is mitigated. Furthermore, it secretes hydrogen and chloride, which may be beneficial in those with renal insufficiency and subsequent preexisting acidosis.[135,136] Serum chloride has been noted to decrease and bicarbonate increase following the use of stomach in the urinary tract.[130,137] The net excretion of hydrogen chloride and acidification of the urine is also able to reduce bacteriuria.[84,115]

Unfortunately, the popularity of the stomach has diminished significantly due to the potential for a profound hypochloremic metabolic alkalosis, hematuria–dysuria syndrome (HDS), and a high risk of malignancy.[115,138–146] Although uncommon, the metabolic derrangment has resulted in death. HDS may occur in up to one-third of patients, and can be debilitating in those with incontinence, normal sensation, and oliguria.[144] If a reservoir is to be constructed from the stomach, the continence mechanism must be 100% reliable, as severe skin excoriation may occur with urinary leakage.[142,143,145] The stomach should be avoided if a period of anuria is anticipated, as the urine is necessary to buffer the gastric acid production, thus preventing irritation and perforation.[138] Pharmacologic therapy with H_2 blockers and hydrogen ion pump blockers may be helpful in reducing acid production.[146–148]

Another disadvantage of the stomach is its contractile activity. Rhythmic contractions are reported in all large series, occurring in up to 62% of patients.[131,140,149] This is partly due to the small wedge segment of stomach actually used. Larger, more rhomboid segments have improved the urodynamics, but contractility can remain a problem, necessitating a secondary augmentation.[113,150]

To mitigate these shortcomings, a composite reservoir can be created using a second, separate segment.[76,151–153] The hypochloremic alkalosis associated with the stomach is offset by the hyperchloremic acidosis associated with small and large bowel usage, creating a more "balanced" reservoir (Figure 58.12). Only a relatively small (8 × 4 cm) gastric segment is necessary to achieve neutrality. Lockhart et al. have demonstrated that larger segments may result in HDS. In 12 patients with long-term follow-up, 11 have normalized their mean serum $HCO_3$1evels. Serum pH levels have also been corrected, and only one patient has had persistent metabolic acidosis.[153] Using a more compliant segment likely will also offset the increased storage pressures. Gastroileal composite reservoirs seem to provide many advantages but take longer to construct, as a second anastomosis is necessary and there is potentially significant blood loss.

The mobilization of the greater curvature along the gastroepiploic artery is also very demanding technically, and results in quite a long transabdominal mesentery. This has been postulated to be the main reason that the author's augmentation series has the greatest risk of bowel obstruction when gastric segments are used.

Finally, the risk of malignant degeneration appears to be very high, as reported by Gozalbez's group (https://www.ncbi.nlm.nih.gov/pubmed/22425048) and others.[154–156] Therefore, the use of gastric segments has fallen out of favor with many, but the University of Cincinnati has shown good long-term outcomes with its composite reservoirs.[157]

Creation of an Antireflux Mechanism

A nonrefluxing ureteral anastomosis is felt to be important in the pediatric patient. While the necessity for this can be debated in the adult patient, concerns over the greater life expectancy and susceptibility of the developing kidney have driven this sentiment. The historic aspects and the various mechanisms were reviewed by Walker.[158] Reimplantation of ureters into gastrointestinal segments can be quite challenging, and although many techniques have been described, all have their basis in the original technique introduced by Coffey.[159] Antireflux mechanisms today are generally based on a mucosal tunneling technique or by the creation of nipples by intussusception.

Le Duc et al. described by an intralumenal tunneling technique, whereby a 3 cm mucosal sulcus is created.[160] The ureter is brought through the bowel wall, placed in this sulcus, and secured. The intestinal mucosal edges are sutured to the ureteral adventitia and, with time, with mucosa will cover the ureter to create a tunnel with muscle backing. Abol-Enein and Ghoneim described an ingenious technique using a serosal tunnel, which is easily constructed and appears to reliably prevent reflux (Figure 58.13).[161]

Nipple valves are generally constructed by intussuscepting ileum or using the ileocecal valve but have had more complications than tunneling techniques and are more difficult to construct. In the authors' experience, there has been nearly a 50% incidence of reflux noted on long-term follow-up in those in whom a reinforced intussuscepted ileocecal valve was used as the antireflux mechanism. A split-cuff nipple valve using ureter has been reported by several authors, and is very easily constructed and surprisingly reliable (Figure 58.14).[114,162,163] Stone and MacDermott noted mild reflux in only 1 of 35 ureters, all of which had at least a 2-year follow-up.[162] This is particularly useful in the dilated ureter, where tunneling techniques are more likely to lead to ureteral obstruction.

Regardless of the technique used, reported results are generally favorable. Walker noted that success rates are slightly worse than reimplanting into native bladder.[158] Most interesting is the report by Lockhart et al., where 165 of 201 ureters were anastomosed end to side with no effort made to prevent reflux.[164] Neither reflux nor obstruction occurred in 87%. Tunneled reimplants have successfully prevented reflux in greater than 95% of patients.

Creation of a Continence Mechanism

Due to the absence of the urethra, the CUR is entirely dependent on a continent catheterizable channel. The creation of the perfect reservoir with no reflux is of no value to the child who continually leaks urine onto the abdominal wall. Difficulty or the inability to catheterize the reservoir puts the child at risk for recurrent infections, renal deterioration, and reservoir perforation. As Benson and Olsson have observed, the integrity or failure of the continence mechanism determines the success or failure of the diversion.[165] Numerous techniques have been described to provide continence, but they all fall basically into one of the following categories: nipple valves, ileocecal valves, and flap valves (Mitrofanoff principle). The reservoir can be catheterized through a segment of ileum or appendix. Some techniques use a combination of these valve mechanisms. Examples of each type will be demonstrated. The interested reader should be aware of two excellent reviews of continence mechanisms by Sagalowsky[166] and Austin and Lockhart.[167]

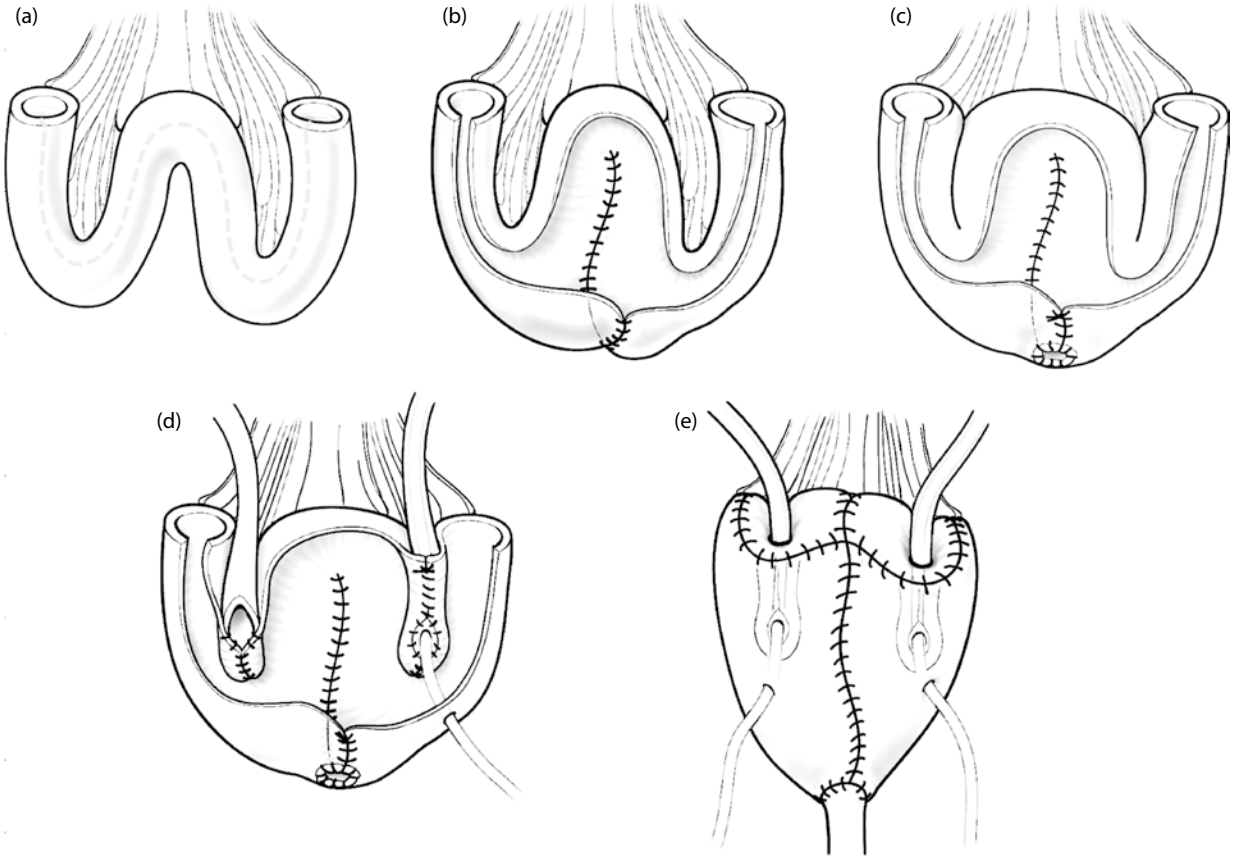

FIGURE 58.13 Abol-Enein and Ghoneium reimplant. (a and b) A W-shaped ileal segment is fashioned and the bowel is opened on the antimesenteric border. (c and d) Two serous lined troughs are created and the ureters are placed in the troughs with the ureteral meatus anastomosed to the intestinal mucosa. (e) The free bowel edges are closed over the ureter, creating a serosal lined tunnel. (Adapted from Abol-Enein H, Ghoneim MA. *J Urol* 1994;151(5):1193–7. With permission.)

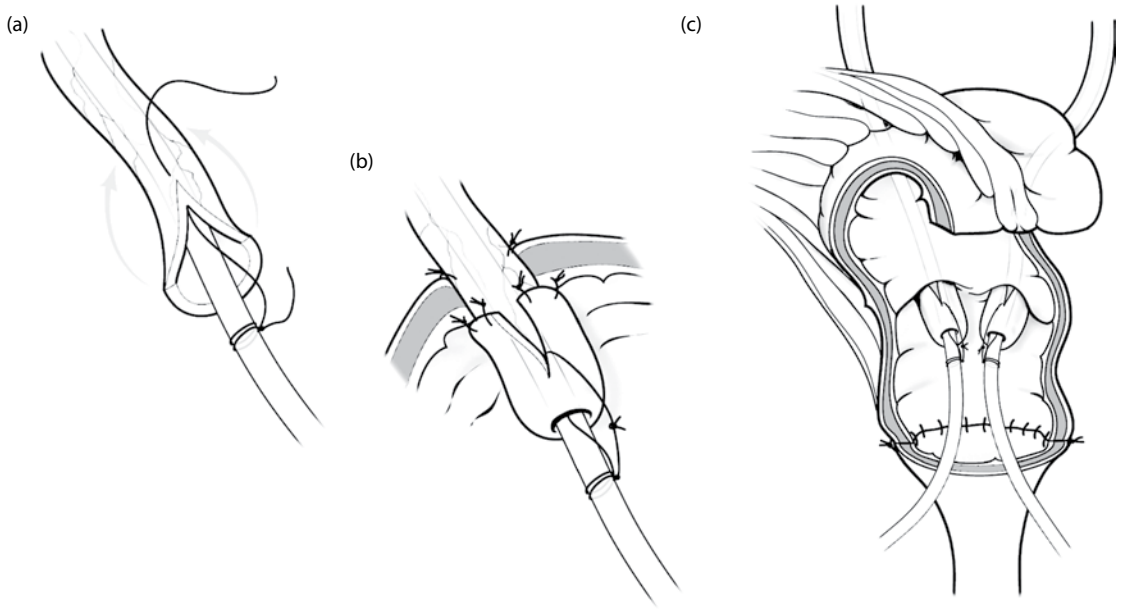

FIGURE 58.14 Split-cuff nipple, created by spatulating and everting the ureter over a stent. They are brought through the bowel wall and secured. (Adapted from Goldwasser B, Webster GD. *J Urol* 1986;135(2):215–24. With permission.)

Ileal Stomas

Nipple Valves

Nipple valves are generally created by intussuscepting an intestinal segment to create a sphincteric compression mechanism via the bowel, and are used in many of the most popular CURs. An ileal nipple is used in the Kock pouch (Figure 58.15) and the Mainz pouch (Figure 58.16). An ileocecal nipple is used in the pouch described by Mansson et al.[168]

When the nipple valve is within the lumen of the reservoir, the principle of equilibration pressures adds further to continence. Unfortunately, the intrareservoir pressure that compresses the nipple to provide continence also applies forces to evert, flatten, or destabilize the nipple (Figure 58.17). Because of the nipple's tendency to fail over time, many ingenious methods to stabilize the nipple have been reported. Hendren described dissecting the mesentery off the ileum to be intussuscepted and scarifying it to provide internal fixation.[169] The Kock pouch has been modified many times from its original application as a continent ileostomy.[170] The procedure reported in the first 12 patients involved the use of 60–70 cm of ileum for the reservoir.[72] The middle 40 cm was folded into a U shape after being opened on its antimesenteric border. In later patients, the nipple valves were constructed by intussuscepting the ileum into the reservoir. The nipples were stabilized by staples, and either Marlex mesh or fascia was positioned as a cylinder around the base of the nipples and secured to the reservoir. One nipple was used for continence and the other to prevent reflux. The Kock pouch has since been popularized by Skinner, who made further modifications.[73] There appears to be a steep learning curve, but in Skinner's hands, the results have been reported to be excellent, with excellent compliance and pouch capacities over 700 mL.[79,73] The large amount of ileum required (78 cm), the complexity of the procedure, and the requirement for two nipples with stapling and collar fixation have deterred its widespread use in children. Hanna and Bloiso achieved success in a small series in children, but modified the nipple to avoid the use of staples and Marlex.[78] Benson and Olsson noted that nipple failure occurs in approximately 15% in the best of hands, and no longer recommend its routine use.[165] The three most common complications are fistulae at the base of the nipple, nipple valve prolapse, and shortening of the nipple length.[79]

Ileocecal Valves

The ileocecal valve is commonly used as a continence mechanism; however, in its native form it is functionally adequate in only 25% of the population.[171,172] Rendelman et al. found that at 25 cmH_2O, the valve is competent in 75%, but only 7% at 50 cmH_2O pressure.[172] Reinforcement to achieve continence was described by Zinman and Libertino by wrapping the cecum around the ileum.[173] Intussusception of the ileocecal valve as a nipple to enhance its continence is the basis for the pouch described by Mansson et al. in 1990.[168] Hussman and Cain reported very good outcomes using a hemi-Indiana pouch.[174] The Mainz pouch (mixed augmentation with ileum and zecum) uses tunneled ureteral implants to prevent ureteral reflux and an unusual nipple valve for continence, with the reservoir created by combining the cecum and Ileum.

To improve results, many groups have described placating the ileocecal valve, and this has become widely accepted as a reliable continence mechanism. The Indiana pouch is based on a modification of Gilcrest and Merricks's cecoileal reservoir. It has undergone several modifications since the initial report in 1985.[175] In this procedure, the cecum is detubularized and used as the reservoir. Reflux prevention is obtained by tunneling the ureters into the tenia or by the Le Duc technique.[176] The continence mechanism is based on plication of the ileum to the level of the ileocecal valve. The native ileocecal valve is reinforced by Lembert sutures (Figure 58.19). A very similar technique has been used by Lockhart et al. in the Florida pouch.[177] The advantage of this procedure is its ease of construction, using techniques familiar to all urologists. Carroll and Presti[230] compared plicated versus stapled ileal segments and noted that mean contraction pressures were higher in the stapled group (63 ± 27 cmH_2O at 41 ± 21 cmH_2O). Mean reservoir volumes were 675 mL, with mean reservoir contractions being 24 cmH_2O and mean plicated ileal pressures 40 cmH_2O in the reservoir. As would be expected from these data, continence rates have been quite good. Rowland reviewed several series and noted that one of 17 patients (6%) required repair of the efferent limb for leakage.[178] Canning, however, reported that leakage occurs more readily with this mechanism than with nipples.[179] Ring and Hensle achieved a 95% continence rate in 29 chi1dren undergoing the Indiana pouch.[180] In Rowland's most recent report, 5 of the last 81 patients had incontinence secondary to high reservoir pressures;[181] however, the cecal reservoir with ileum may correct this.

Koff et al. reported a technique to provide hydraulic compression to the efferent ileal limb of the Indiana pouch.[182] A segment of ileum is used to wrap around the efferent limb and is anastomosed to the cecal pouch. While this would increase resistance further, it adds complexity to an otherwise easily performed procedure that already has a high continence rate. Koff's approach has not gained widespread use.

Appendiceal Stomas

Imprication

Many centers now take advantage of the in situ appendix, which can be imbricated into the cecum, as the continence mechanism (Figure 58.18). Stein et al. reported on 116 patients who catheterized via an imbricated appendix, where only 6.7% had early complications, 25% late complications, and all patients were continent.[183] Gerharz et al. compared the continence mechanisms and noted that 12% of the nipple valves required revision, compared with 17% of the appendiceal stomas. However, the majority of the appendiceal revisions were relatively simple cutaneous revisions for stomal stenosis, while the nipple valves were much more complex and required a laparotomy.[184] Therefore, the imbricated appendix is now their preferred catheterizable channel. If the appendix is not available, a Lampel tube of cecum can be used (Figure 58.19b).[185]

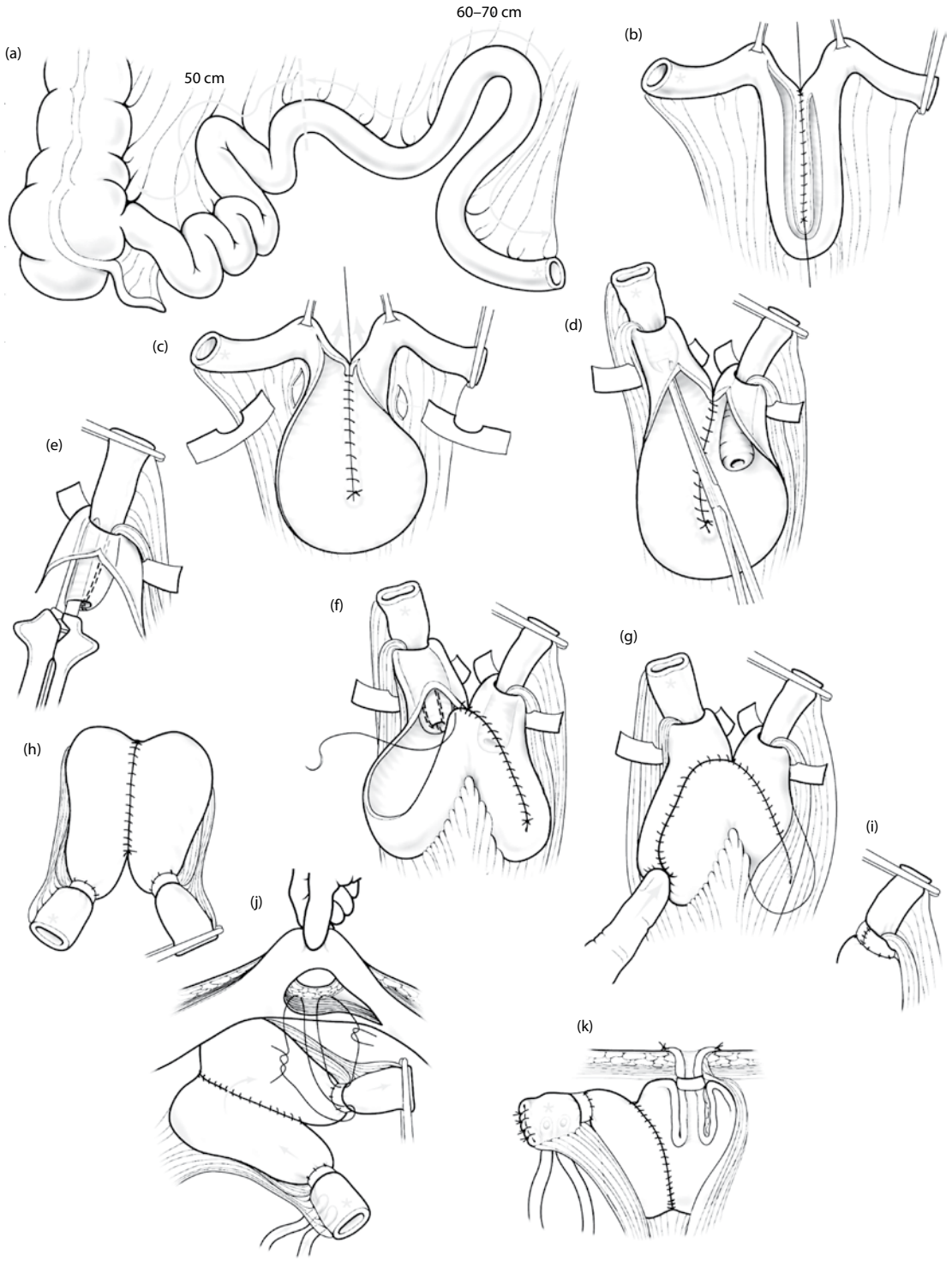

FIGURE 58.15 Kock pouch (continent ileal reservoir). (a) Bowel segment measuring 60–70 cm is isolated approximately 50 cm from the ileocecal valve and positioned as the letter U with the terminal end directed toward the head of the patient and the bottom of the U toward the left side of the patient (https://www.ncbi.nlm.nih.gov/pubmed/1502742). (b) The legs of the U are united at the antimesenteric border with continuous 3–0 polyglycolic acid sutures. (c) The intestine is divided adjacent to the suture line and the incision is continued for 3 cm on the afferent limb. The mucous membrane is sutured with continuous 3–0 polyglycolic acid sutures. Openings are made in the mesentery supplying the future base of the nipple valves. (d) Intussusception of the afferent and efferent segments into the future reservoir. (e) The nipple valves are secured with staples. (f) The reservoir is closed with two continuous inverting 3–0 polyglycolic acid sutures. (g–h) The reservoir is brought into its final position by pushing the corners of the reservoir downwards between mesenteric leaves. (i) A fascia of Marlex mesh encircles the base of the nipple valve, and the ends are approximated with three or four non-absorbable sutures. The reservoir wall is sutured to the cylinder with 3–0 polyglycolic acid sutures. (j) The cylinder at the efferent segment is attached to the opening and anterior rectus sheath with non-absorbable sutures. (k) The completed continent ileal reservoir.

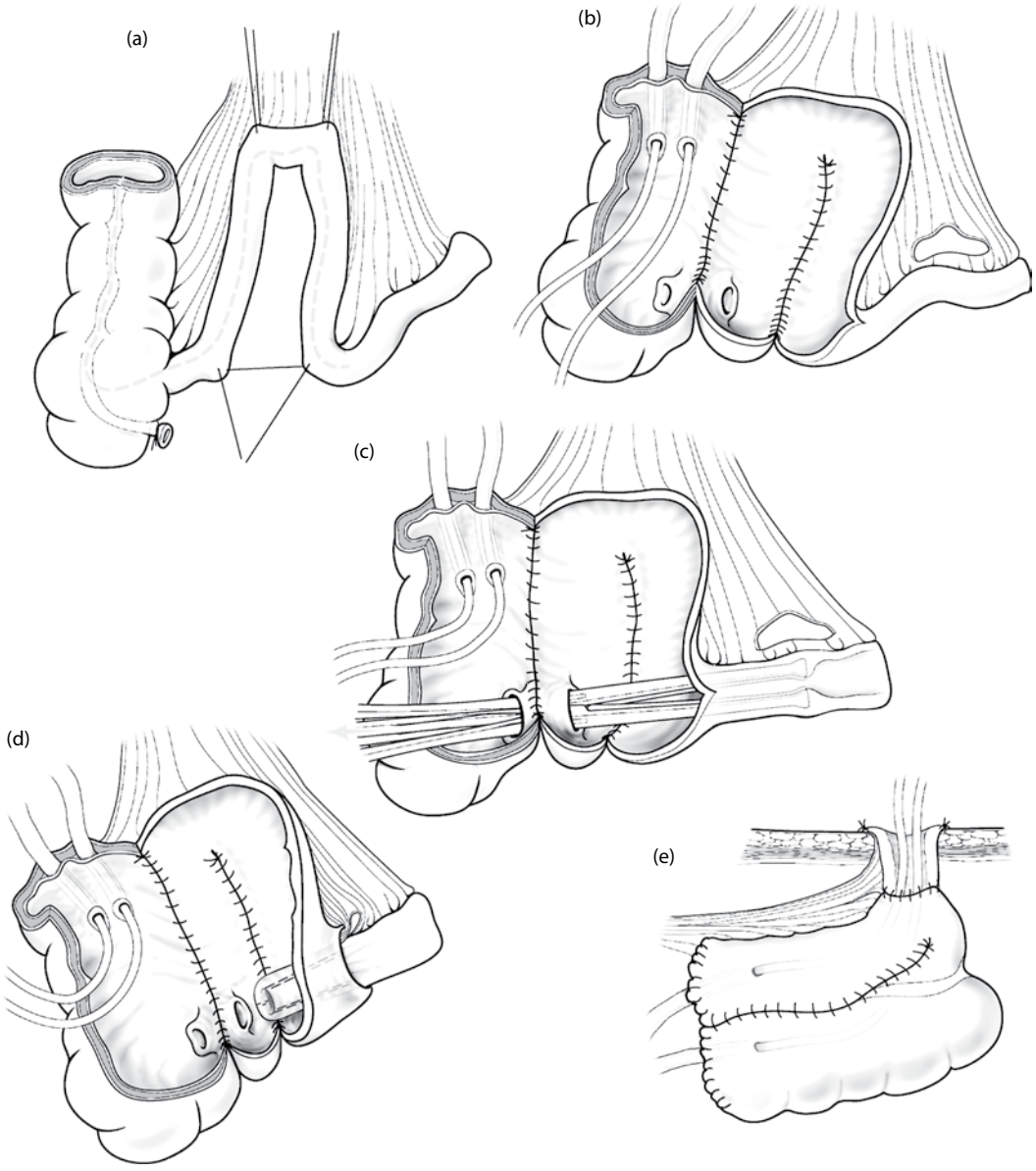

FIGURE 58.16 The Mainz pouch utilizes intussuscepted ileum pulled through the ileocecal valve (c) as the continence mechanism.

Reimplantation

Without question, the most commonly used continence mechanism in children is based on the flap valve principle, as introduced by Mitrofanoff (Figure 58.20).[186] He reported the use of the appendix to tunnel into the neuropathic bladder (similar to a ureteral reimplantation to prevent reflux) to provide a continent catheterizable stoma into the native bladder. The procedure was popularized by Duckett and Snyder,[187,188] who extended the use of this technique to create a continent ileocecal pouch, the Penn pouch (Figure 58.21).[189] Since these early reports, many authors from around the world have reported their experience using not only appendix but also ureter; tapered ileal, colonic, or gastric tubes; fallopian tubes; and vas deferens.[190–199] The continence mechanism is based on placing a supple tube in a submucosal tunnel with a 5:1 ratio of length-to-tube diameter. Firm muscle backing of the tube prevents reflux. It was initially thought that the tube itself must also be muscular, but bladder urothelium, colonic mucosa, and preputial skin alone have all been used successfully.[200–202]

This is a relative simple procedure using techniques familiar to pediatric urologists. It is also particularly useful in children who, as noted previously, often are not candidates for use of the ileocecal valve or long segments of ileum. Kaefer and Retik reviewed several series and found that continence rates ranged from 86% to 96%.[196] The most common complication reported is stomal stenosis. Khoury et al. noted stomal stenosis in 5%–57% of patients and described a technique of placing the stoma at the umbilicus.[203] The Mainz group concluded that the stomal stenosis is slightly higher when placed at the umbilicus. A high risk for stenosis has also been seen when using the appendix compared with tapered ileum; however, this

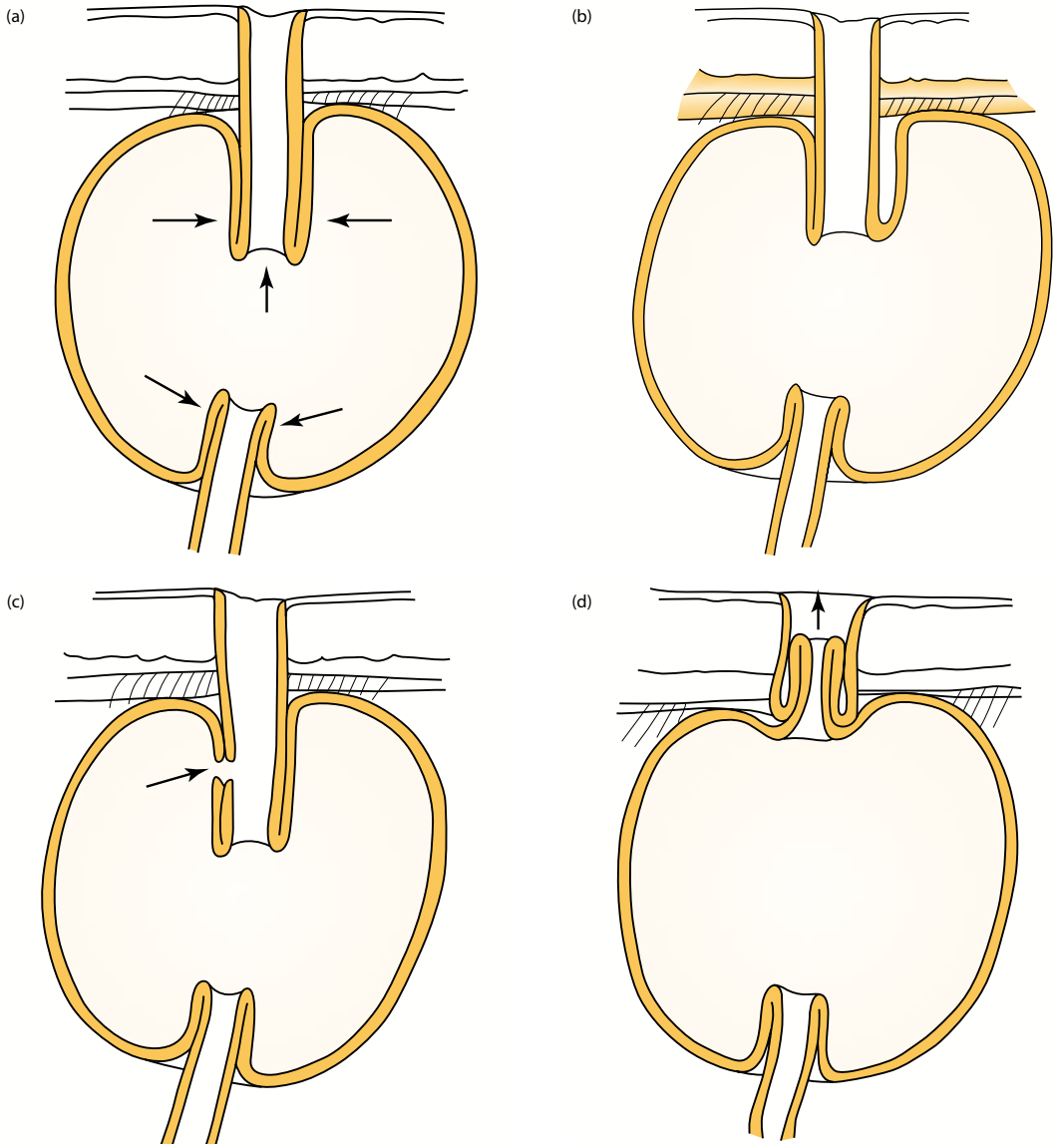

FIGURE 58.17 Nipple valves. (a) Hydrostatic forces exerted on the nipple to provide continence. (b) Breakdown of nipple, yielding incontinence. (c) Fistula of nipple, yielding incontinence. (d) Prolapse of nipple, resulting in inability to catheterize.

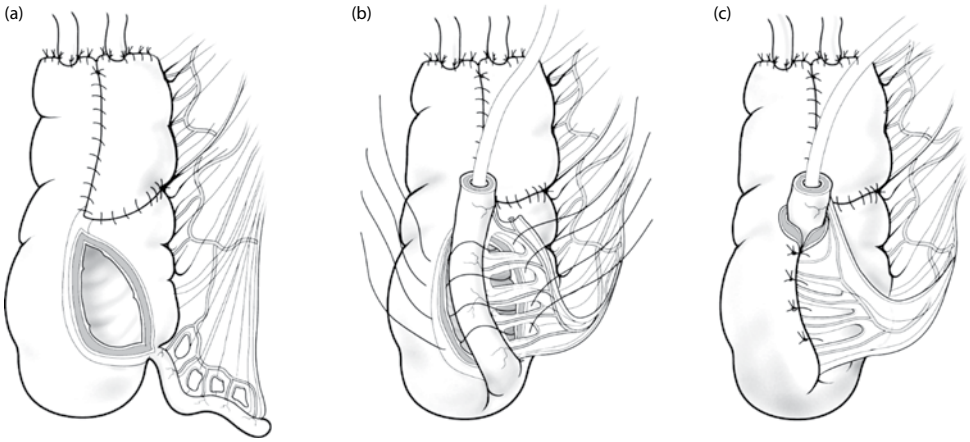

FIGURE 58.18 Mainz pouch with appendix. (a) The cecum has been patched with ileum. A seromuscular incision is made in the tenia. (b) Mesenteric windows are made in the mesoappendix. (c) The appendix is placed in the submucosal tunnel and the cecum is closed over it, avoiding the appendiceal vasculature.

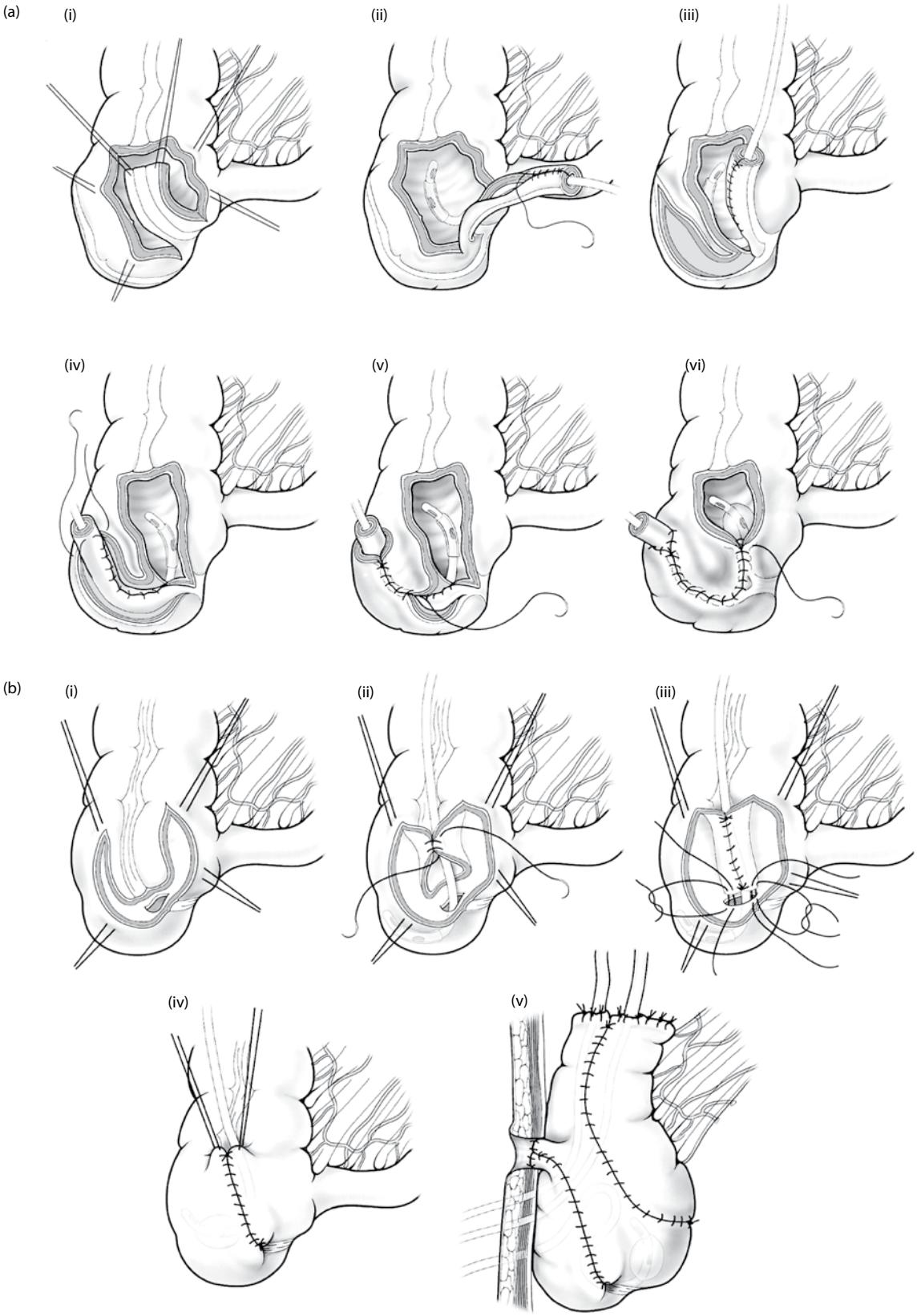

FIGURE 58.19 (a) Lampel tube. (i–iii) A full-thickness bowel flap is elevated and tubularized over an 18 Fr catheter. (iv–vi) It is then placed in a submucosal subtineal tunnel and the bowel wall is closed. (b) Lampel seromuscular tube. (i and ii) The elevated seromuscular layer is tubularized over an 18 Fr catheter and (iii) anastomosed at its base to the mucosal opening. (iv) The bowel wall is closed over the tube and (v) brought to the umbilicus as a catheterizable stoma. (Reproduced from Lampel A et al. *J Urol* 1995; 153(2):308–15. With permission.)

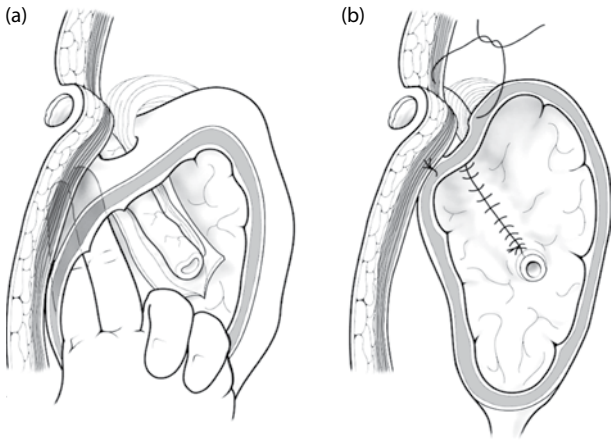

FIGURE 58.20 Appendicovesicostomy is performed by tunneling the appendix submucosally into the bladder. (Reprinted from Keating MA, Rink RC, Adams MC. *J Urol* 1993;149(5):1091–4. With permission.)

difference was not seen in the largest published series from Indiana University.[204,205,208] The Great Ormond Street group has reported a decrease in the incidence of stomal stenosis using a VQZ skin-flap technique.[206] Using the concealed umbilical stoma technique, the Pittsburgh group has seen a stomal revision rate of 7% at nearly 3 years' mean follow-up.[207] At a minimum, a skin flap should be placed into the spatulated tube. In the authors' last 100 patients in whom the Mitrofanoff principle has been applied, there is a 99% continence rate. Stomal stenosis has occurred in 12% (5/57 appendix, 1/22 ileum, and 6/21 bladder).[208] In the Boston experience, 5 of 50 patients leaked at the stomal level, 5 had stomal stenosis, and 1 had an appendiceal stricture.[196]

Since the introduction of the Malone antegrade colonic enema (MACE) procedure, which used the appendix brought to the skin for irrigation of the cecum to treat constipation, it has become necessary to find other tissue to form a catheterizable urinary stoma. The recent description of the Yang–Monti technique,[209,210] which uses only 2 cm of reconfigured ileum to form a

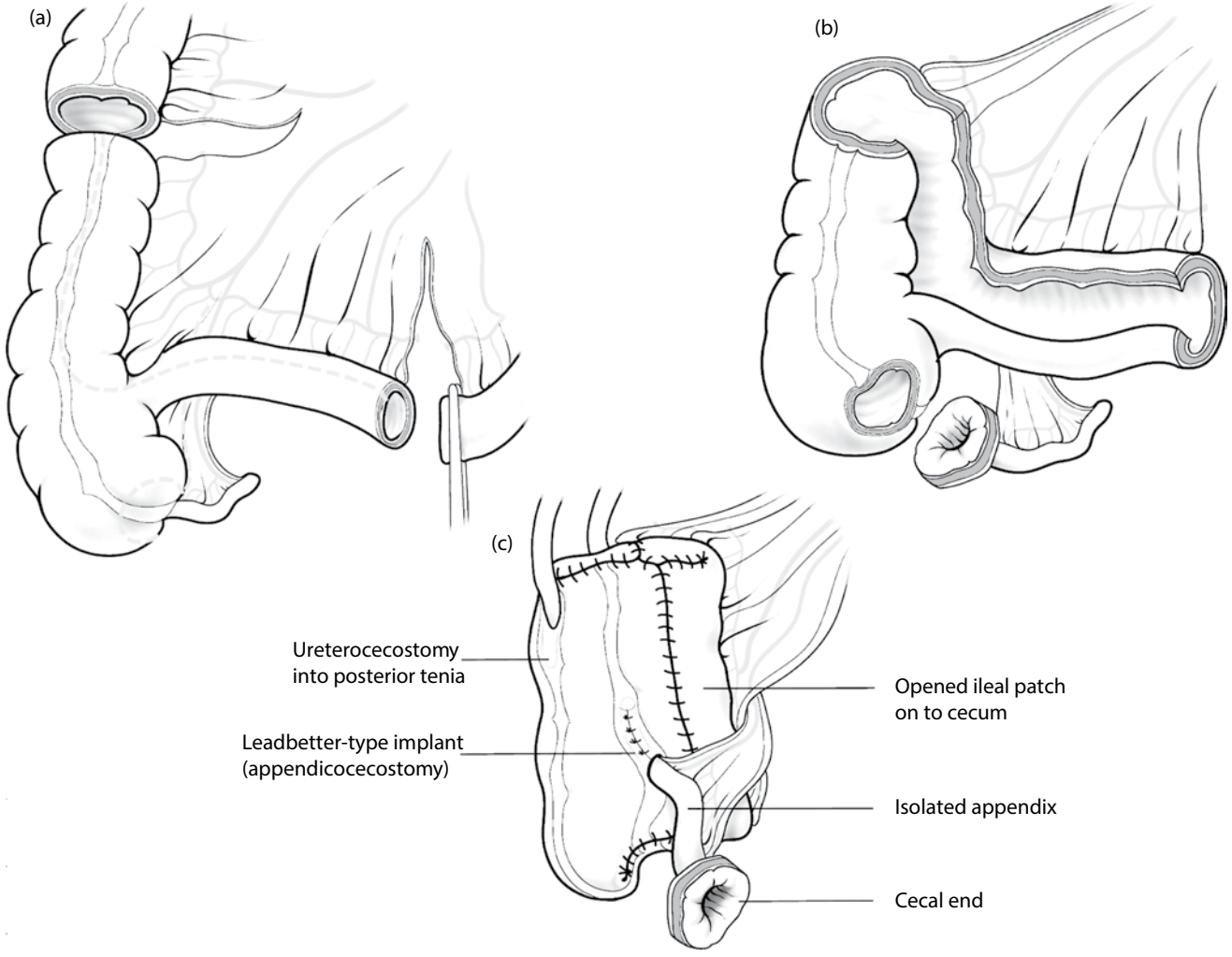

FIGURE 58.21 The Penn pouch. (a) The ileocecal segment is isolated and incised on its antimesenteric border; the ureters are implanted into the colonic segment. (b) The appendix is isolated in its mesentery. (c) The ileocecal segments are joined and the appendix is implanted into the cecum; the cecal end is brought to the skin as a catheterizable stoma.

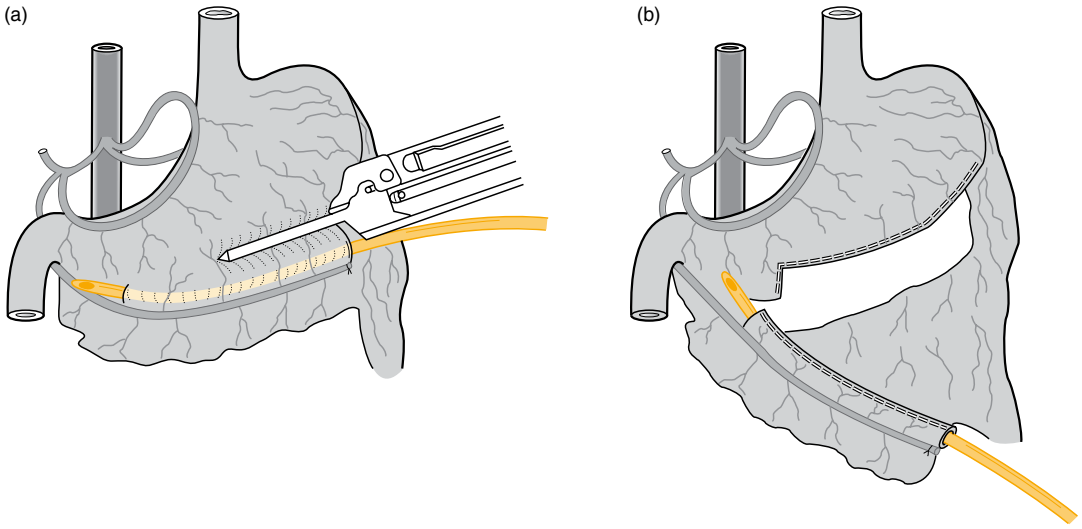

FIGURE 58.22 (a) An isolated gastric tube is harvested with a GIA-90 stapler over a 12 Fr catheter. (b) The mobilized isolated gastric tube is ready for placement into an augmented bladder or reservoir.

tube, has been a great advance and used successfully (Figure 58.23).[211] Tunneling of these tubes into colon or stomach is easily accomplished but is difficult in ileum. A seromuscular trough for implantation has been described,[194] and Plaire et al.[212] have described a serosal reimplant similar to the Abol-Enein and Ghoneim ureteral reimplant (Figure 58.14). It is now clear that the Mitrofanoff principle is a major advance and that virtually any supple tube placed in a tunnel that has adequate muscular backing will successfully provide continence (Figures 58.26 and 58.27).

Ureterosigmoidostomy

The only reservoir that provides a volitional continence mechanism, which also happens to be the first continent reservoir, is the ureterosigmoidostomy.[213] Since its introduction, more than 60 modifications have been proposed. Because of the problems with upper tract deterioration, occasional incontinence, acidosis, and the risk for adenocarcinoma, it has been largely abandoned. However, the opportunity to control continence without CIC continues to make it very attractive. It cannot be used in spinal dysraphism, as a neurologically intact anal sphincter is required. Therefore, in children it has been used almost exclusively in the exstrophy population when continence with CIC is not possible or continence cannot be achieved with bladder neck surgery. It has been suggested that oatmeal enemas be given preoperatively to check anal continence.[214]

Classically, ureterosigmoidostomy has been done by simply tunneling the ureters into the rectum. However, the risk of cancer at the anastomotic site and nighttime incontinence led surgeons to pursue other efforts to provide more of a reservoir effect and avoid direct contact of the ureters with the stool. Development of neoplasms seems to require urine to be in contact with stool and bowel mucosa.[215,216] Of 94 children with ureterosigmoidostomy followed at the Children's Hospital of Boston, 7 developed adenocarcinoma of the colon, 4 of whom died.[217] Rink and Retik

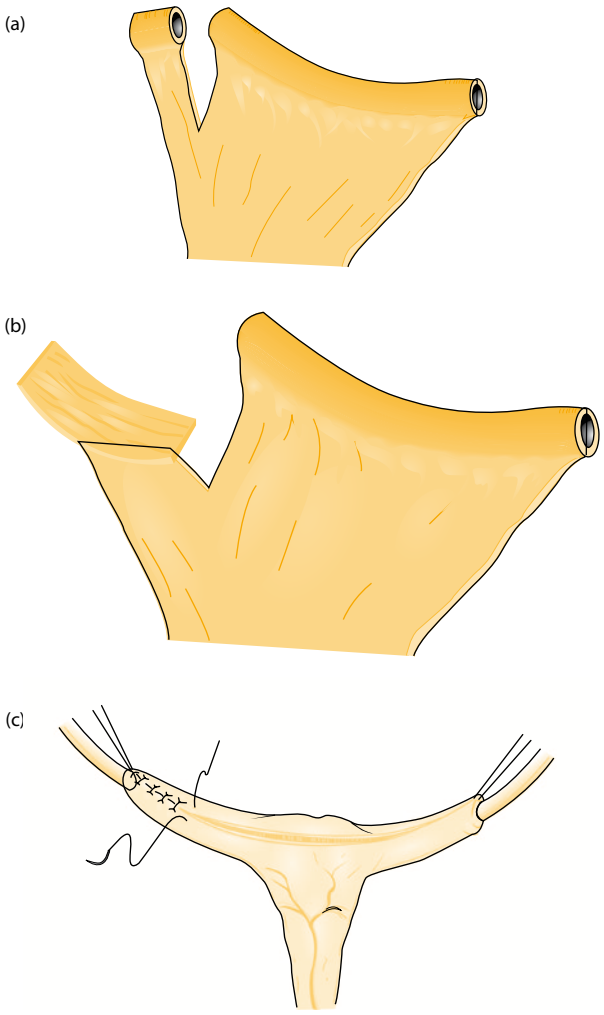

FIGURE 58.23 Yang–Monti. (a) A 2 cm segment of small bowel is isolated on its mesentery. (b) It is opened on its antimesenteric border. (c) The segment is retubularized by closing it in a longitudinal fashion (see also Figures 56.23 and 56.24).

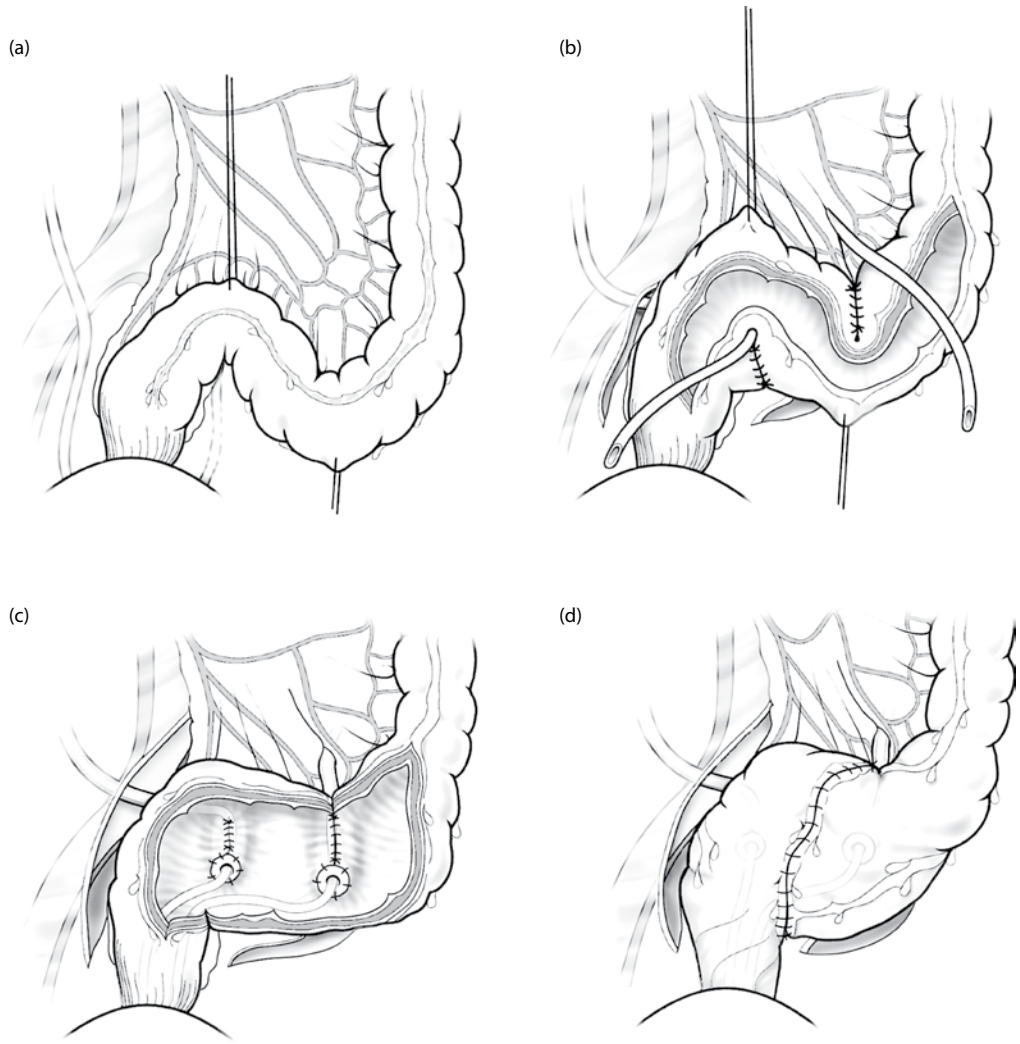

FIGURE 58.24 The Mainz pouch II (sigma rectum) has been presented as a means of reconstructing a low-pressure ureterosigmoidostomy. (From Djokić JH et al. *Acta Chir Iugosl* 2014;61(1):29–34. https://www.ncbi.nlm.nih.gov/pubmed/25782222.)

proposed that an ileocecal conduit be initially constructed and the conduit later anastomosed to the intact sigmoid by end-to-end colocolostomy.[218] Kock et al. described a "valved rectum" with the colon intussuscepted at the rectosigmoid junction to prevent reflux of rectal contents and an ileal patch anastomosed to the anterior rectal wall.[219] This allowed the rectal capacity to increase from 200 to 700 mL, with maximal pressures of only 24 cmH_2O and minimal metabolic disturbances.[219]

A hemi-Kock pouch anastomosed to the rectum has also been described,[219] but the complexity of creating the colonic nipple in these two procedures makes them less attractive. The sigma rectum (Mainz pouch II) has been proposed from the Mainz group as a means of lowering the very high pressures in the intact rectosigmoid colon without the need for nipples or augmentation (Figure 58.24).[220] Continence was achieved in 40 of 47 patients, with voiding five times per day, and extracolonic pressures remained low. The results in 34 patients of the Mainz II were reported by Gerharz et al.[221] All were continent during the day. One had nighttime soiling and creation of an ileal conduit due to recurrent septicemia. One ureteral obstruction led to a nephrectomy, and two had mild hyperchloremic acidosis. While lower pressures with the new procedures should reduce the risk for upper tract changes, the risk for adenocarcinoma still weighs heavily when contemplating any type of ureterocolonic diversion.

Postoperative Care

The complexity of the repair and the potential for complications demand diligent postoperative care in the immediate and long-term periods. In the early postoperative interval, externalized ureteral stents are required to divert the urine from the fresh ureteral-enteric and CUR anastomoses for at least 1 week. H_2 blockers are given temporarily if stomach is used. A large-bore (20–24 Fr) silastic suprapubic tube and a 12–14 Fr catheter in the channel ensure maximal drainage of the reservoir and will remain in situ for 3 weeks. The reservoirs are gently irrigated to remove mucus and prevent plugging of the catheters three times a day for the first 3 weeks, and then slowly decreased to daily, for the rest of the patient's life. A pouch-o-gram may be obtained before removal of the stents.

The patient and all primary caregivers are seen in the outpatient clinic 3–4 weeks from the date of surgery. The catheter is removed and the family is taught CIC through the channel. The indwelling reservoir drainage (suprapubic) tube is only removed after they have demonstrated that they can easily catheterize the stoma and empty the reservoir. Demonstration of complete emptying is mandatory to prevent long-term problems of infection, stone formation, incontinence, and perforation, and to maintain stable renal function. Antibiotics are given until all tubes are removed. The family is to catheterize every 2 hours for the first week, then every 3 hours, and then every 4 hours by the third week. They may then gradually increase the intervals overnight (daytime frequency remains at 4 hours), until it is possible to go the entire night without pain or leakage.

It should be reinforced with the caregivers that the sensation of the reservoir is associated with the gastrointestinal tract. This means that when the CUR is distended, and needs to be catheterized, the patient will not feel a "full bladder" but will often complain of a "full tummy." A distended reservoir will often protrude and be visibly distended.

If the patient or caregiver is unable to catheterize the reservoir, the patient must be seen and the situation addressed urgently. Cystoscopic assistance may be required to reinsert a catheter, or a suprapubic tube be inserted with ultrasound guidance.

The family must be aware that sudden or severe abdominal pain may result from a rupture of the CUR, and this is a life-threatening event. This can be very subtle in the neuropathic populations, as their sensation is impaired and presentation can be delayed.

Renal and pouch sonography, abdominal radiographs, and serum creatinine and electrolytes are all obtained 3 months postoperatively, repeated at 6-month intervals twice, and yearly thereafter. Vitamin B_{12} levels should be checked in the long term and somatic growth monitored. Endoscopic evaluation of the pouch should be carried out annually starting 5–10 years postoperatively.[222–224] Cytology has also been proposed to detect any malignant degeneration.[225] However, these strategies have not yet demonstrated any benefit in the early detection of malignancies.[225]

SUMMARY

Tremendous advances have been made in lower urinary tract reconstruction in children. The entire urinary tract can now be completely replaced, with continent bladders, nonrefluxing ureters, and transplanted kidneys. Incontinent cutaneous diversion is an extremely useful temporary measure of urinary drainage and is easily reversed once the child and family are prepared for continent diversion. However, several permanent options also exist for scenarios where the patient and caregivers are unwilling or unable to provide the care required for a continent diversion.

Although it may be ideal to maintain the native urinary tract intact, if this cannot be achieved, a CUR should be considered. The limits of reconstruction are based only on the surgeon's imagination and skills. As long as the principles of CUR construction outlined in this chapter are met, a successful surgical result can almost always be achieved. True success, however, will always require the cooperation of a well-motivated child and equally motivated parents.[226] Furthermore, the type of major reconstruction necessitates that the surgeon be surrounded by dedicated personnel who function as a team for the betterment of the health of these children.

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CHAPTER 59

The Malone Antegrade Continence Enema (MACE)

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INTRODUCTION

Congenital anomalies of the bowel and urinary tract frequently coexist, and constipation by itself may produce significant bladder dysfunction, leading to incontinence and urinary tract infection.[1] As a result, the pediatric urologist must be conversant with bowel problems and play an active role in their management. Both systems should always be assessed simultaneously, and with present surgical techniques, it is the urologist who is often best placed to treat both urinary and fecal incontinence synchronously.[2]

The first antegrade continence enema (ACE) or Malone (MACE) procedure was performed in 1989, in an attempt to treat the intractable fecal incontinence associated with spina bifida. Koyle et al. subsequently introduced the technique in North America in 1991.[3] Malone et al.[4] reported that 53% of young adults with spina bifida suffered from fecal incontinence, and similar results have been reported by Holschneider[5] in patients with anorectal anomalies, many of whom also had neuropathic bladder dysfunction.[6]

The MACE combined three well-recognized surgical principles that have been clearly described in many papers and the previous editions of this book, and will not be described in detail again here. The combination of these principles, applied to the colon, provided continent intermittent catheter access to the cecum or proximal colon for the administration of antegrade enemas while the patient sat on the toilet. This produced colonic emptying and fecal continence. The preliminary series was reported by Malone et al.,[7] and subsequently, numerous reports have been published so the procedure is now widely practiced around the world.[1,3,8–12] Many modifications have been introduced following the original description,[13] to both simplify the procedure and reduce the high complication rates initially reported.[8] This chapter reviews the techniques in current use, the medical management of constipation, patient selection and preparation, the enema regimens, and the most recent results.

MEDICAL MANAGEMENT

As is the case in any other surgical condition, careful thought and consideration must first be given to more conservative, nonoperative means of treating intractable disorders of defecation. A medical plan, consisting of dietary changes, oral laxatives, and retrograde enemas is often sufficient to manage patients with chronic constipation. In patients with intractable constipation, it is important to ascertain whether an enema program would be beneficial before definitive surgical therapy is instituted. Matsuno et al.[14] suggested in a recent study that fecal continence was comparable whether the enema is administered rectally or antegrade. However, procedural independence was significantly better in the group performing antegrade enemas.

The pediatric surgery group from Cincinnati Children's Hospital Medical Center has devised a bowel management protocol using retrograde enemas to treat patients with fecal incontinence due to either constipation or a tendency toward diarrhea.[15] Prior to beginning any maintenance enema protocol, the rectosigmoid should not be severely impacted. If it is, disimpaction should be performed with multiple daily enemas, oral laxatives, or even manually under anesthesia if needed in extreme circumstances. Once disimpacted, the program is initiated and lasts 1 week. It consists of seeing the patients daily, monitoring the amount of colonic stool with daily abdominal radiographs, and modifying the volume and content of the retrograde enemas to suit the individual needs of each patient. Normal saline is used as the solution, and additives of glycerin (5–30 mL), liquid soap (91–18 mL), or phosphate are added to the solution, in that order (from least to most irritating), when needed to obtain the desired effect. Fleet's phosphate was added for the most difficult patients. The dosage used is 30 mL (half of a pediatric Fleet's) for children <4 years old, 60 mL (full pediatric Fleet's) for children 4–10 years old, and 120 mL (adult Fleet's) for children >10 years of age. The volume of the enema must be tailored to effect, with constipated patients requiring 500–1000 mL on average. Management is considered successful when the underwear remains clean for 24 hours. A 98% (217/220) success rate was reported in their constipated patients. Accordingly, they have stressed the importance of attempting to achieve a successful nonoperative result before consideration of a MACE. Given this high success rate, their approach to intensive medical bowel control is warranted. The enema formulation itself, not the route of administration, should

be considered the key determining factor for a successful outcome.

PATIENT SELECTION AND PREPARATION

For those in whom more conservative measures fail, retrograde enema compliance becomes an issue, and in those who experience successful bowel management through rectal enemas, but desire or require a more convenient means of administration, surgical MACE creation should be discussed. The underlying diagnosis is important, as it influences the success rate. In the initial Southampton experience, patients with a neuropathic bowel and anorectal malformation had a success rate of 73% compared with 38% for patients with chronic idiopathic constipation.[16] Most subsequent worldwide experience similarly has shown that those whose primary bowel problem is constipation fare worse than those with other elimination problems. In part, this might be secondary to the spastic pelvic floor and sphincter, and/or the bowel motility issues themselves. These results have been mirrored by the wider experience in the United Kingdom, where a success rate of 91% was also reported for patients with Hirschsprung's disease.[17] Recent personal communications from pediatric surgery colleagues suggest that the results for patients with chronic constipation have improved. Kokoska et al.[18] reported significant improvement in 10 and continence in 6 of 11 children undergoing a MACE procedure for chronic constipation. The age at operation was also important. In Southampton, there was a 70% failure rate for patients under 5 years of age compared with 24% for those aged over 5 years, a highly significant difference.[16] This was independent of the underlying diagnosis, and it probably reflected the inability of a child under 5 years of age to sit on a toilet for up to 1 hour before emptying is complete. Christison-Lagay et al.[19] reported that age under 12 years was another predictor of success, and Gerharz et al.[20] showed high failure and complication rates when performed in adults. In that study, patient and caregiver motivation was vital in determining success. A lack of compliance to the washout regimen was a major contributory factor to failure in nine patients in our early experiences. Detailed preoperative counseling and continued postoperative support, ideally provided by a nurse practitioner, are essential to ensure adequate and continued motivation, without which the MACE is doomed to failure. It is an advantage to introduce the potential patient to a child and family with a functioning MACE prior to the surgical procedure.

In summary, the ideal patient for a MACE should be between the ages of 5 and 12, have a diagnosis of neuropathic bowel, have an anorectal malformation or Hirschsprung's disease, be well motivated with a dedicated family, and have tried and failed all conservative measures first.

OPERATIVE TECHNIQUES

An aggressive preoperative bowel preparation is essential to facilitate the initial postoperative enema. A cleanout from below is often necessary, especially in the patient where constipation is the primary problem. Appropriate prophylactic antibiotics are always administered perioperatively. A bowel prep is up to the judgment of the surgeon and is not mandatory. In most instances, since coincidental urinary tract reconstruction is performed, a lower midline or Pfannenstiel incision is selected, depending on the patient's body habitus, prior surgical scars, and preference. The open approach can be combined with preliminary laparoscopy, as this allows laparoscopic mobilization of the colon, and is especially useful when the right colon has become more adherent cranially in the abdomen, often to the liver. In such cases (often the spina bifida patient who has prior abdominal incisions and a ventriculoperitoneal shunt), a large incision is avoided. In the patient in whom a MACE only is indicated, a laparoscopic or percutaneous approach or an appendectomy incision can be employed.

In Malone's initial description of the technique, the appendix was transected from the cecum and then reimplanted in an antireflux manner into the teniae. This was based on the concept that creating a valve mechanism would result in no leakage of bowel contents via the cutaneous stoma. Few surgeons perform the MACE in this fashion any longer. Rather, the in situ appendix can be folded over with the cecal wall wrapped around it to produce the antireflux mechanism. This is an adaptation of the technique originally described for the Mainz pouch urinary reservoir.[12] This procedure is performed in slightly different ways depending on the surgeon. Koyle simply wraps the cecal wall around the folded appendix using permanent sutures, similar to the technique for a Nissen fundoplication. On the other hand, Malone continues to produce a submucosal tunnel along one of the tenia and inlays the appendix into this, finally closing the seromuscular layer over it with absorbable sutures (Figure 59.1). The authors recommend catching the serosa of the appendiceal wall with covering sutures in order to prevent it from pulling out of the tunnel. The mesentery of the appendix is fenestrated to prevent the wrap from compromising the blood supply to the appendix. Currently, both of these techniques are performing satisfactorily without significant long-term leakage. Once the antireflux mechanism has been constructed, the cecum or colon is sutured to the posterior aspect of the anterior abdominal wall to ensure that the conduit is not lying free in the peritoneal cavity, as this can lead to kinking and difficulties with catheterization.

It has been reported that it is not necessary to construct an antireflux mechanism, and some surgeons simply pull the appendix out to an abdominal stomal site. This may be done using a laparoscopic approach.[21] We have attempted not using an antireflux mechanism on a number of occasions, and in some cases, the stoma was incontinent of flatus and/or stool, but in the majority, the stoma was continent. Other groups have retrospectively compared laparoscopic ACE (LACE) with and without cecoplication, and have found no increase in stomal incontinence.[22,23] Lawal et al.[24] challenged the previous thinking that an antireflux mechanism could be omitted laparoscopically due to technical difficulty, and showed that cecal plication is feasible with a laparoscopic-assisted approach, and virtually eliminates the risk of stomal incontinence. We continue to recommend that an antireflux mechanism be constructed.

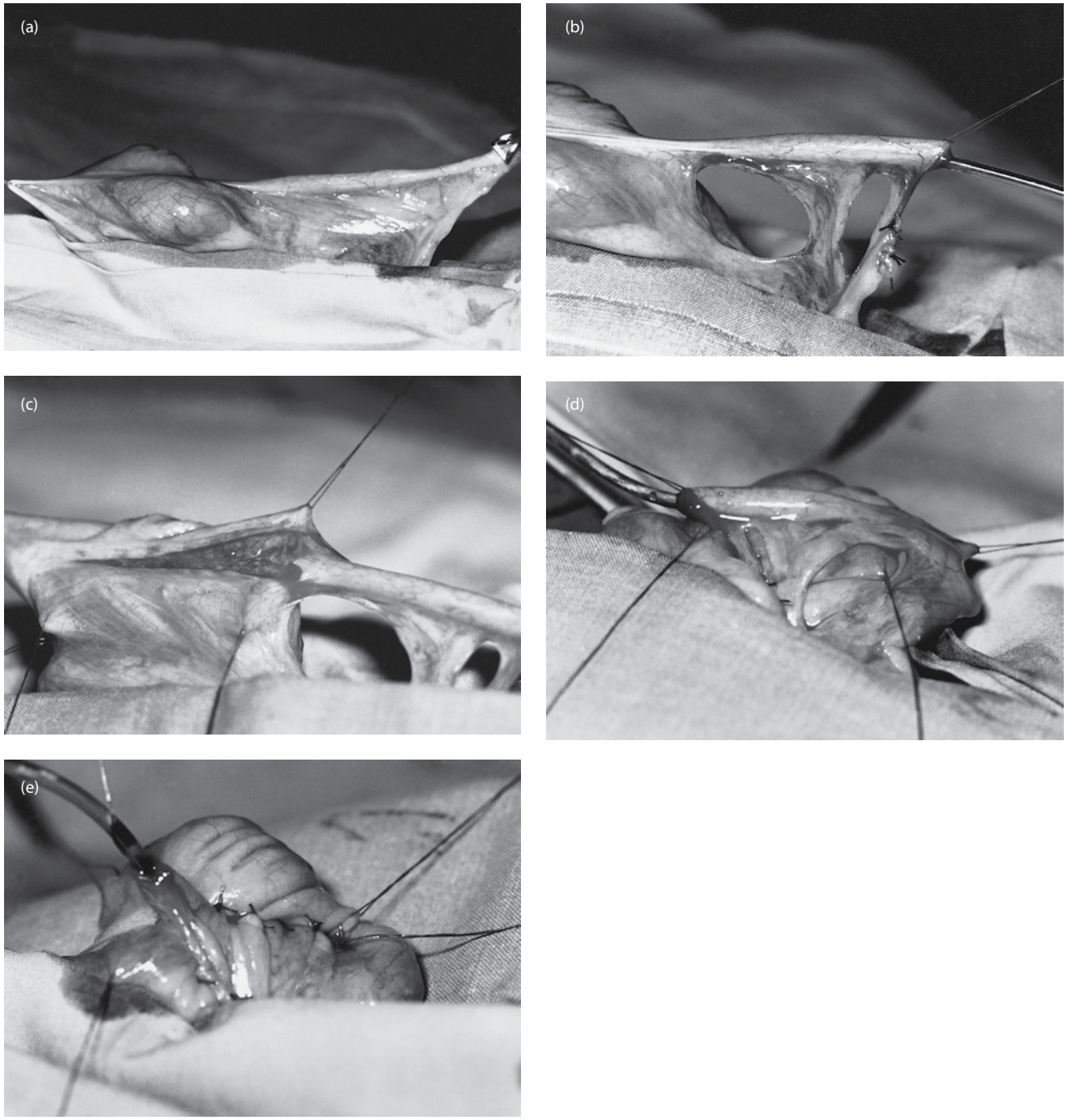

FIGURE 59.1 In situ formation of the MACE. (a) In situ appendix attached to the cecum. (b) Fenestrated appendix mesentery. (c) Submucosal tunnel along one of the tenia. (d) Appendix folded into the tunnel. (e) Completed tunnel (note the short length of the appendix).

The technique needs to be modified if simultaneous MACE and appendicovesicostomy procedures are being performed. If the appendix is long enough and the vascular anatomy is suitable, it is possible to split the appendix, and we have done this successfully. If the appendix is not suitable to split or is absent, another technique must be instituted. The tubularized cecal or colonic flap[25] was previously not recommended because of the unacceptably high complication rates associated with this technique.[3] More recently, it has been suggested that a colon flap or cecal extension of an unacceptably short appendix can be done with relative ease, good results, and improved complication rates.[26] There are two additional alternatives to the appendix worthy of serious consideration. The first is the Monti procedure.[27] This is an ingenious technique where a segment of ileum is harvested on its pedicle and transversely detubularized on its antimesenteric border. The rectangular patch is tubularized along its longitudinal

axis to create a catheterizable conduit of approximately 7 cm in length. The internal valvulae conniventes run in the longitudinal direction of the conduit, thus facilitating easy catheterization. Both ends of the conduit are free of mesentery, and this makes the creation of the antireflux mechanism easy. When a Monti conduit is used, the Mitrofanoff flap valve principle is followed and a submucosal tunnel is created along one of the tenia, which is wrapped around the conduit. This is similar to the original description of the MACE.[13] If the patient is obese, it is possible to use two segments of ileum or colon and produce a 14 cm conduit ("the full Monti"), which is long enough for virtually all patients. This is the procedure of choice when the appendix is not available.[28]

The other technique worthy of consideration is the use of a cecostomy tube and cecal button. Shandling et al.[29] initially described a technique for the percutaneous placement of a cecal tube that could be changed at a later date to a low-profile cecal button (similar to a gastrostomy button), which is then used to administer the enema. A number of patients in our series manage their MACEs using a button, with results no different than those using an appendiceal MACE (Figure 59.2). The indications for the button were

- Sloughing of cecal tubes formed when the appendix was absent
- Refusal by children or caretakers to catheterize their stomas, and thus the buttons are being used semipermanently in these cases
- Patients who developed stomal stenosis on at least one occasion and the families have preferred the nonoperative button option to that of repair under anesthesia

Our greatest worry has been erosion or skin problems as the abdominal wall girth increases with age; hence, a close follow-up is mandatory. The tubes are unsightly, and occasionally leakage around the tube will occur that leads to embarrassment. In a survey of 300 MACE procedures performed in the United Kingdom, 19 cecal buttons were used, and they worked well in most cases.[17] Chait et al.[30] placed buttons percutaneously under local anesthesia with good results, and follow-up data of a 7-year experience showed successful placement in all 163 procedures, with outcomes similar to those of other approaches.[31] The same procedure has been performed laparoscopically during concomitant appendicovesicostomy in three patients without any differences noted.[32] It is our subjective impression that in the long term, many of the patients with stomal appliances develop skin problems and leakage and, as a result, or because of pure image issues, request formal conversion to a bowel-based MACE.

One of the problems encountered in some patients with the MACE, particularly those with constipation, is the time it takes for the washout to work. This has led to failure and abandonment of the procedure in a number of patients.[9] In an attempt to overcome this problem, some surgeons have placed a Monti-MACE conduit in the left colon to reduce the length of bowel that has to be washed through, and thus the time taken. Preliminary results with this approach are very encouraging and show similar results with equivalent complication rates compared to traditional MACE.[33–37] In addition, a recent literature review showed that left-sided conduits had less enema fluid requirements, shorter transit time, and fewer complications when compared with right-sided conduits, with comparable outcomes.[38] A left MACE should always be considered in patients with severe associated constipation. More recently, a new development embracing the principles of minimally invasive surgery and the left-sided MACE has occurred. Following bowel preparation, a colonoscopy is performed. With the scope in the distal descending colon, a colostomy tube is inserted as one would insert a percutaneous endoscopic gastrostomy (PEG), the percutaneous endoscopic colostomy (PEC), with washouts being able to commence the next day. We have used the percutaneous tubes as "training wheels," especially in constipated patients. In such cases, when it is uncertain where the enema should be administered, an initial tube is placed in the right colon. If the flushes are successful clinically, then the patient and family may wish for no further surgery or desire conversion to a formal MACE. If the results, however, are inadequate, a second tube can be inserted into the left colon or sigmoid. If results are better than on the right, a left-sided MACE is then offered.[39]

There are therefore a number of different approaches to the MACE in 2014. If the patient requires a synchronous bladder reconstruction, a formal conduit is constructed using the in situ appendix in the cecum, or a left-sided Monti-MACE if constipation is a severe problem. If the MACE is all that is required, a LACE would be the procedure of choice for cecal placement, or a PEC if the patient is constipated and a left-sided placement is needed. Now, it is also easy to perform simultaneous MACE and Mitrofanoff urinary diversion, offering patients the chance of complete continence for the first time.[2,40,41]

By adopting these newer techniques, complications such as incontinence of the conduit or difficulties catheterizing it are rare. However, another potential complication is conduit perforation and intraperitoneal instillation of the enema. DeFoor et al. retrospectively reported a 3.7% risk of perforation in 187 patients between 1989 and 2002. Seven patients presented with abdominal pain and/or traumatic catheterization, two requiring laparotomy for peritonitis. The remaining patients were managed with endoscopic placement of a catheter for a 6-week period.[42]

The remaining aspect of the operative technique is the construction and placement of the stoma. The most common complication of the MACE in our earlier series was stomal stenosis. Curry et al.[16] reported an incidence of 55%. Nineteen and twenty-two percent of the patients in our initial series required surgical revision. In an attempt to reduce this stenosis rate, patients were advised to intubate the stoma twice a day, and this seemed to be reduce the problems with stenosis. The initial description of the MACE advocated a cutaneous V-flap, but we changed to using modifications of the Ransley VQZ-flap when the MACE was positioned in a location other than the umbilicus to try to reduce the incidence of stenosis still further. This has been shown to significantly reduce stomal problems in the Mitrofanoff,[43] as well as the MACE procedures.[44] This method uses two separate skin flaps and can be constructed on the abdominal wall or in the umbilicus (Figure 59.3). The conduit is left intubated for a period

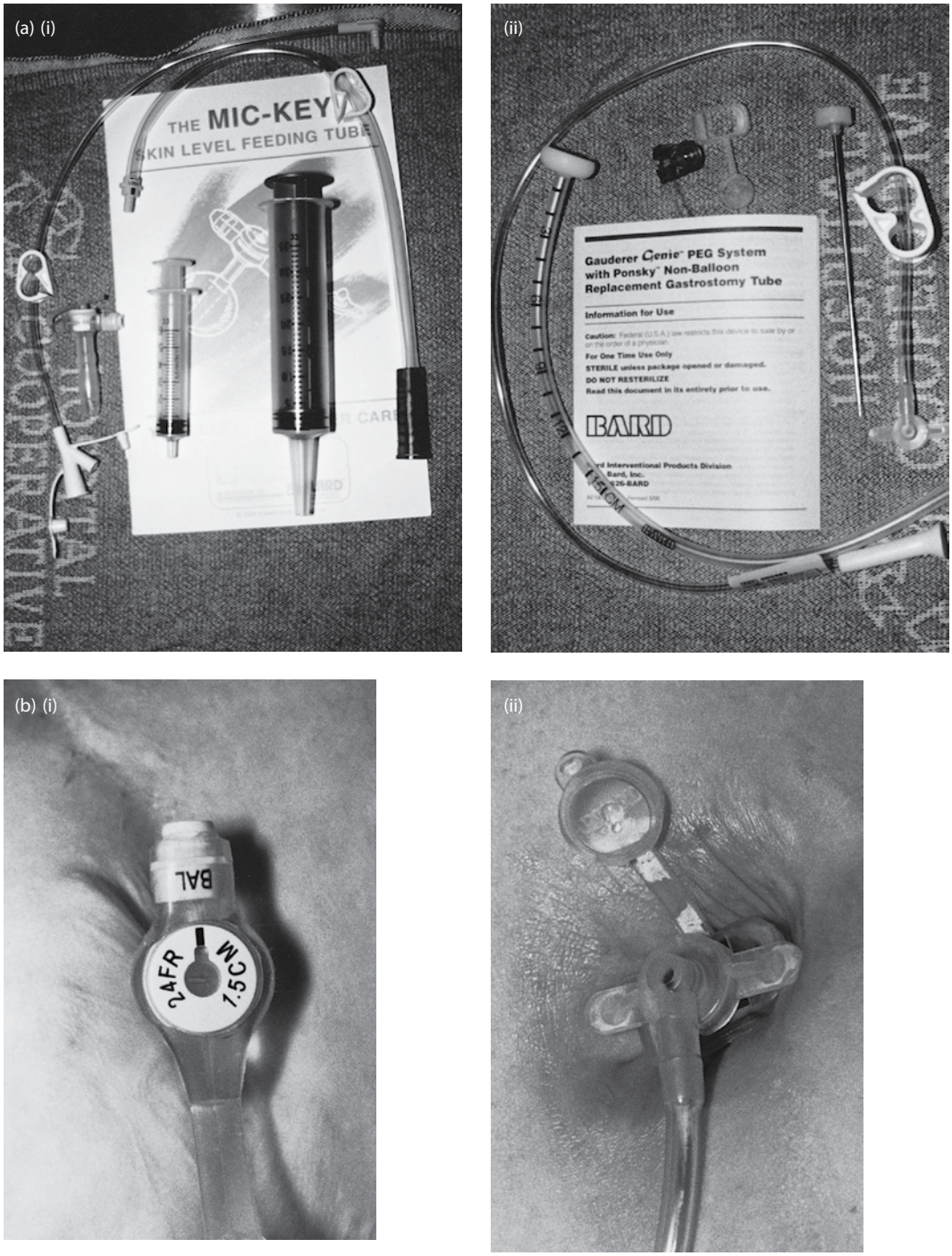

FIGURE 59.2 (a) (i) Mic-Key (Ballard Corporation). (ii) Genie (Bard) button kits. (b) (i) Mic-Key button in right lower quadrant MACE stoma. (ii) Genie in umbilical stoma.

of 2–4 weeks postoperatively before intermittent catheterization is begun. McAndrew and Malone[45] reviewed their experience of all continent catheterizable conduits. They found no difference in the complication rates between the Mitrofanoff or MACE procedures. Ninety-seven percent of the conduits were continent, and the stomal stenosis rate was 31%. There was no difference relating to the type of conduit or the site of the stoma. Stomal stenosis occurred in 41% of V-flap stomas and 25% of modified VQZ-flap stomas, and although this did not reach statistical significance, there was certainly a trend in favor of this stoma. Barqawi et al.[46] reported very similar results, with a continence rate of 98% and a stomal stenosis rate of 18%. More recently, Landau et al.[44] demonstrated superiority of the VQZ-flap when compared with umbilical stomas or tubularized skin flaps, with no stomal complications reported.

In summary, these data suggest that the ideal MACE should use the in situ appendix or the Monti conduit with

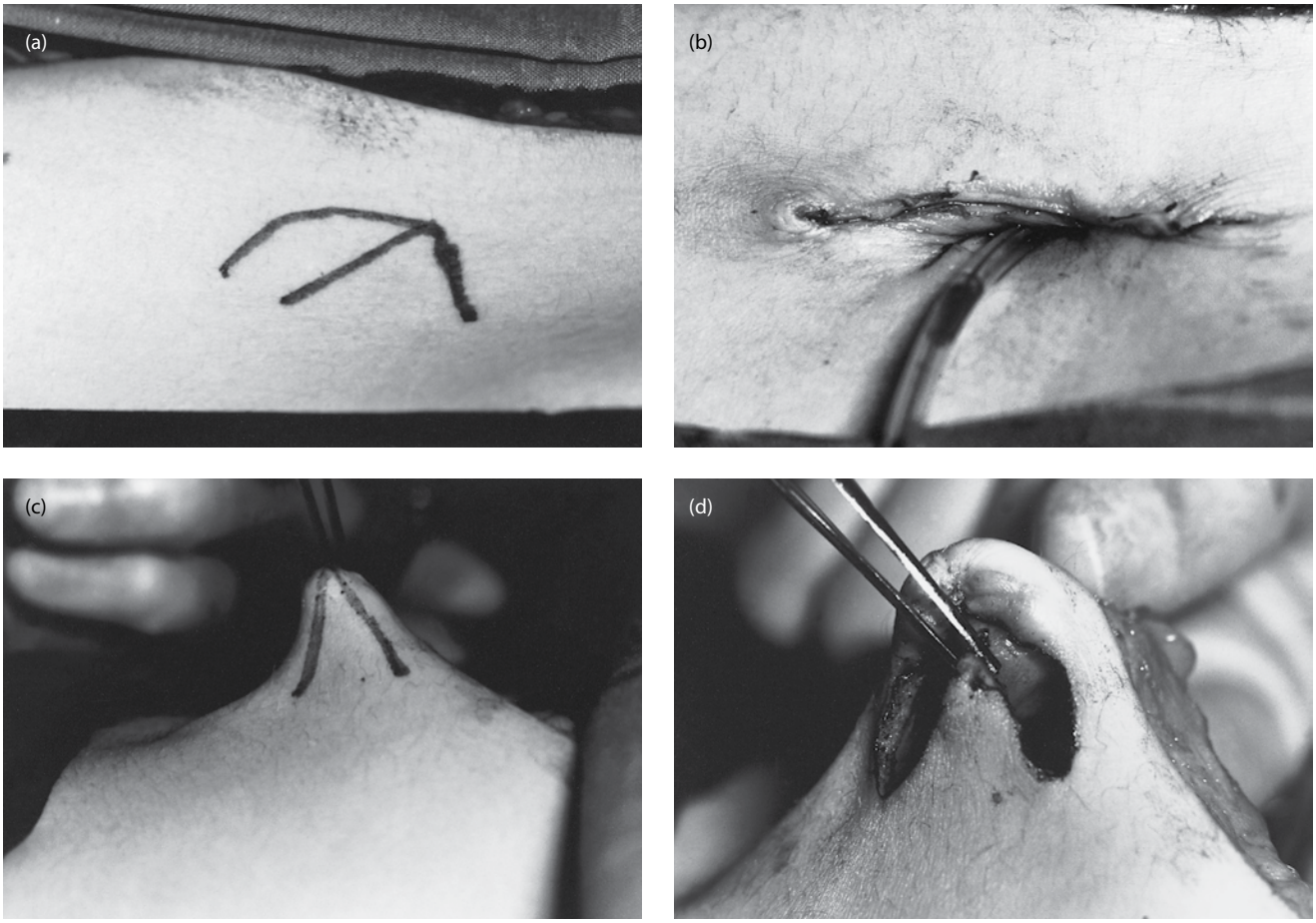

FIGURE 59.3 VQZ right lower quadrant (VQZ) and V-flap umbilical stomas. (a) Multiflap VQZ abdominal stoma. (b) Complete VQZ stoma in the right lower quadrant. (c) Everted umbilicus for the V-flap. (d) Mobilized V-flap. Note that this produces a second anterior flap.

an antireflux mechanism. A two-flap cutaneous stoma should be used and placed either on the abdominal wall or in the umbilicus.

ENEMA REGIMEN

The first enema is given via the indwelling catheter when bowel activity returns, usually around the third to fifth postoperative day. In those patients whose primary problem is constipation, it may be necessary to clean out the bowel from above and below initially, until an effective MACE regimen has been achieved. The time of day that the enema is administered is patient dependent, and most families prefer to give the enema during the early evening hours, just after dinner. This time is chosen to allow a sufficient interval to achieve the desired result before bedtime.

Many enema regimens are used in the different centers performing the MACE, and patients frequently modify them to suit their own particular needs. One of the most important points is to advise patients not to expect immediate success. Each individual regimen usually takes up to 1 month to figure out, and is established by trial and error. In our series,[16] many children did not achieve a steady state or a successful MACE for periods of up to 6 months. It is necessary to counsel patients about this preoperatively, as early disappointment can lead to complete failure. Many patients experience a degree of rectal leakage within the first few hours of the washout, but this is rarely a major problem. While the washout regimen is being established, it is vital to maintain regular contact with the nurse specialist. Initially, daily washouts are recommended, but once the patients are comfortable with the procedure, they may attempt to decrease the frequency to alternate days. Once a steady state has been achieved, there is no benefit from interfering with the regimen. In our series, the mean time taken to perform the washout was 39 minutes (range 20–60 minutes) and 34 minutes (11–68 minutes), respectively. It is essential that patients and caregivers be aware of the time commitment that is required and be prepared to devote this time to bowel care, because if they do not, the MACE will fail. Because patients have to sit on the toilet for a long time, one of the complications encountered is pressure sores on the buttocks. It is possible to obtain padded toilet seat covers, and their use is recommended, particularly for the neuropathic patient with reduced or absent sensation.

The enema given differs from center to center, with most centers in the United Kingdom favoring the use of a stimulant, while those in the United States use mainly saline or tap water. In the United Kingdom, the common

regimen uses a phosphate enema (Fletchers, Pharmax, United Kingdom). Initially, 50 mL of enema solution is made up to 100 mL with tap water (this has replaced the saline initially used), and this is rapidly instilled, followed by approximately 500 mL of water. Depending on the response, adjustments are made to the strength and volume of the phosphate, up to a maximum of 100 mL of undiluted phosphate enema. Although a few patients achieve successful results with the phosphate alone, the majority require the additional water lavage. Care must be taken when using phosphate, and the dose will need to be adjusted, depending on the age of the child. If the enema does not produce a result, a second one should not be given, as phosphate toxicity may occur if it is retained, and this is a potentially life-threatening complication.[47] Three patients in our early series had experienced phosphate toxicity. Schreiber and Stone reported a case of fatal hypernatremia in a child whose irrigant was tap water with table salt used as an additive, occurring 5 months postoperatively.[48] Yerkes et al. showed safety in using hypotonic tap water as the solution for the washouts without finding water intoxication in any patient. They studied 71 patients, and did not demonstrate any significant hyponatremia or hypochloremia.[49]

If the enema does not produce an immediate result, patients should be advised to wait 1 hour and then perform a further water lavage. If that is unsuccessful, they should be admitted to a hospital for a retrograde enema and observation. However, care must be taken irrespective of the agent used, as there are anecdotal reports of deaths occurring when too much salt was added to tap water. In the United States, tap or salt water is instituted at 50 mL/day and increased by doubling the volume every 3 days until reliable evacuation occurs. If there is no success after reaching 500–600 mL, alternatives are sought, including mineral oil, GoLYTELY or Fleet's enema through the MACE, or altering the frequency of the enema.

Several difficulties have been experienced during establishment of the MACE. The most common problem has been pain during the enema, which occurred in 58% of patients in our early UK series.[16] In the majority of patients, the pain subsided during the first 3 months, but it persisted and was a major contributory cause to the failure of the MACE in three patients. Strategies for the reduction of pain include lowering the concentration of the phosphate, reducing the rate of the infusion, using an antispasmodic prior to the enema, or changing the enema agent to a licorice root solution, which produces less peristalsis than the phosphate. Three inches (7.5 cm) of licorice root or 5 mL of commercially available licorice granules are microwaved with 100 mL of saline until the mixture boils. It is allowed to cool to room temperature and then is diluted with a further 200 mL of saline prior to administration. It is also possible to vary the concentration of the licorice, depending on the response and whether the patient experiences pain. Many patients in the United Kingdom are now successfully using this regimen, and it does seem to produce much less pain. It is also possible to use many of the other laxatives, such as bisacodyl or docusate sodium, by instilling them directly into the colon via the MACE. In North America, where balanced fluids are primarily used, pain has been less of a problem. Usually, reducing the volume of infusate or the route of administration alleviates the problem.

Despite regular washouts, some patients get constipated, and this produces pain and washout failure. Under these circumstances, a Fletchers' arachis oil retention enema (Pharmax) instilled 12 hours before the washout was recommended, but because of possible peanut allergy, this has now been replaced by mineral oil. In the United Kingdom, saline enemas by themselves have been tried, but this seems to lengthen the time taken to achieve a successful washout, and the authors continue to recommend a stimulant such as phosphate or licorice.

One of the problems encountered with the MACE is the time taken for the enema to pass and achieve a result, more than 1 hour in some cases. In our series,[16] the most common cause of failure was the inability to pass the enema, which occurred in 9/12 (75%) cases that failed. Also, if passage time has been greater than 45 minutes, compliance, and hence success, was also reduced. The constipated, as opposed to the incontinent, group clearly comprises the majority of these patients. It is in these patients that the left-sided MACE is to be recommended, preferably commencing with a trial of the PEC tube, as described above.[35,36]

Liloku et al.[36] described six patients with a left Monti-MACE, with a washout time of 10–30 minutes, with five being clean. Churchill et al.[37] reported 18 patients with a left-sided MACE with a mean washout time of 18 ± 12 minutes and an 83% continence rate.

In summary, many different enema regimens exist, but they are all established in the individual patient by a process of trial and error and may take up to 6 months to stabilize. The frequency of the enema should not be less than alternate days, and patients should be prepared to spend up to 1 hour on each enema.

RESULTS

The results of the MACE have been classified as follows:[16]

- *Full success*: Totally clean or minor rectal leakage on the night of the washout
- *Partial success*: Clean but significant rectal leakage, occasional major leak, still wearing protection, but perceived by the parent or child to be an improvement
- *Failure*: Regular soiling or constipation persisted, no perceived improvement, and the procedure was abandoned, usually to a colostomy

Curry et al.[16] reported on 31 patients with a mean follow-up of more than 3 years. The MACE failed in 12/31 (39%) patients, and this included 5 of the 8 patients treated for chronic idiopathic constipation and 1 patient with Hirschsprung's disease. When patients with neuropathic bowel and anorectal malformation were analyzed separately, partial and full success rates were 75% and 70%, respectively. Curry and Malone[17] reported on a survey of MACEs performed by members of the British Association of Paediatric Surgeons (BAPS), in which 300 cases were identified and the success rates were dependent on the original diagnosis (Table 59.1).

TABLE 59.1 MACE: Success and failure based on original diagnosis

Diagnosis	Full success (%)	Partial (%)	Failure (%)
Spina bifida	63	21	26
Anorectal	72	17	11
Hirschsprung's	82	9	9
Constipation	52	10	38
Other	44	25	31

The overall success rate, including full and partial success, for this large national series was 79%. It is also interesting to note that complication rates were lower than those in earlier historical series. In particular, the stomal stenosis rate was down to 30%.

Shankar et al.[50] assessed the results of 40 patients who had a MACE more objectively by using a quality of life improvement (QOLI) score. A score of 5 denoted a perfect result, and the mean score for all patients was 3.5. They found the score to be significantly lower in wheelchair-dependent patients with spinal dysraphism (2.5) when compared with all other mobile patients.[4] Aksnes et al.[51] reported important improvements in self-esteem and psychosocial function in 20 patients with myelomeningocele 6 months after a MACE procedure. More recently, Ok and Kurzrock[52] utilized the validated fecal incontinence and constipation quality of life (FICQOL) questionnaire to obtain objective data on patients with spina bifida. They showed a decrease in the number of accidents per week (0.3 vs. 3.9), a decrease in the number of patients needing oral laxatives (6% vs. 44%), and reduced anxiety and family worry, allowing for a greater ability to leave the home without worrying about the child having leakage of stool. Also, Hoekstra et al.[53] demonstrated a satisfaction rate of 86% using a nonvalidated questionnaire, and 73% of their respondents would recommend the procedure to others with intractable defecation disorders. By using these objective measurements, the MACE has been shown to be successful.

Finally, it is valuable to assess those patients undergoing synchronous bladder reconstruction and MACE procedures. Wedderburn et al.[2] reported fecal and urinary continence in 76% of 46 patients undergoing synchronous procedures, but the rate of revision surgery was high. Kajbafzadeh and Chuback[54] reported similarly good results for synchronous surgery, with all 40 of their patients being clean and dry, and an overall 7.5% complication rate. Casale et al.[41] also reported excellent fecal and urinary continence rates in their cohort of 158 patients undergoing total continence reconstruction (both bowel and bladder), and showed no statistically significant difference in the continence or complication rates when compared with those undergoing staged reconstruction.

CONCLUSIONS

Despite the relatively high complication rates, the MACE offers in excess of 80% of patients with neuropathic bowel and anorectal malformation a chance to be clean. When successful, it transforms patients' lives, and it does not interfere with the final option of a colostomy, should that become necessary. No patient should undergo lower urinary tract reconstruction without a complete bowel assessment, and if necessary, a simultaneous MACE should be carried out. A simultaneous procedure does not jeopardize the success of either individual component, and double continence rates range from 76% to 100%. The reconstructive urologist is the best person to manage the bowel, as the operative techniques involved are those routinely employed in lower urinary tract reconstruction. Furthermore, the infrastructure should be in place for meticulous follow-up. This combined approach has been shown to enhance the quality of life for these sometimes complex patients.

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CHAPTER 60

Minimally Invasive Approaches to Lower Urinary Tract Reconstruction

Glenn Cannon, Steven G. Docimo, and Christina Kim

INTRODUCTION

In the past 35 years, minimally invasive surgery in pediatric urology has evolved from simple diagnostic procedures to a method for performing complex reconstructive surgery. The goals of laparoscopy and robotic surgery are to maintain the principles of open procedures while minimizing morbidity for the patient. This chapter discusses the indications, techniques, and outcomes for minimally invasive lower urinary tract reconstruction.

PRINCIPLES OF BLADDER RECONSTRUCTION

Pediatric lower tract reconstruction is commonly indicated for patients with neurogenic or nonneurogenic voiding dysfunction associated with high pressures, low volume, or inadequate outlet resistance. In order to protect the upper tracts from damage, and to enhance or enable urinary continence, surgery is sometimes necessary to enlarge the bladder and lower the filling pressures. In addition, surgery is sometimes necessary to enhance outlet resistance and provide for methods of emptying.

Bladder enlargement may be achieved with or without the use of bowel segments. If a bowel segment is needed, it is detubularized and reconfigured to minimize internal contractions and maximize volume.[1,2] When the circular muscle fibers are divided in a longitudinal fashion, the source for the strongest generation of contractions is stopped.[3] Theoretically, detubularization doubles the volume of the original segment. Although studies have shown the detubularized segments ultimately retain some internal contractions, detubularization is the best method available to decrease its frequency and strength.[4]

Emptying the bladder regularly will reduce the risk of infections and protect renal function. Emptying may be through voiding or may require intermittent catheterization. Catheterization may be achieved through the native urethra or a constructed continent stoma.[5] If bladder outlet resistance is low, this can be treated with bladder neck reconstruction, insertion of an artificial sphincter, placement of a periurethral sling, or bladder neck closure—and intermittent catheterization allows a tight reconstruction without regard to the ability to void spontaneously.

Benefits of Laparoscopic Reconstruction

By creating a continent system, bladder reconstruction allows the patient more independence and better quality of life. Traditionally, the most common way to access the appendix, small bowel, stomach, and colon, as well as other pelvic organs, was by making a long midline incision.[6,7] Laparoscopic reconstruction or assistance allows the same access and manipulation through 5 mm ports with or without a lower midline or Pfannenstiel incision.

The number of visible scars has been shown to inversely correlate with pediatric patients' level of happiness and satisfaction.[8] In addition, scars associated with reconstructive surgery have been associated with lower self-esteem and poor body image.[9] It is reasonable to consider that these associations and outcomes are even greater in the pediatric and adolescent populations. Not only surgical scars, but also the appearance of stomas can have an impact. The development of a concealed umbilical stoma is a major step toward improving body image,[10] as well as decreasing the likelihood of stomal stenosis.[11]

Laparoscopy is associated with decreased morbidity and improved cosmesis. The outcomes in pediatrics have mirrored the outcomes in adults. The use of laparoscopy has been associated with lower narcotic requirements, shorter hospital stays, and quicker return to normal activities. In addition, and perhaps more important to long-term health, it has been shown that fewer adhesions develop after laparoscopic surgery than after open surgery.[12–14]

Most minimally invasive bladder reconstruction falls into one of three categories: laparoscopic, laparoscopic assisted, or robotic assisted. This chapter reviews the principles, techniques, and outcomes of these surgeries.

Indications and Contraindications

As previously noted, the primary indications for bladder reconstruction in children are to improve bladder filling pressures, improve urinary continence, and reduce the incidence of urinary tract infections. Candidates usually have reduced bladder capacity, poor bladder compliance, uninhibited

detrusor contractions, and/or inadequate bladder neck resistance. Options for bladder expansion include autoaugmentation, ureterocystoplasty, and enterocystoplasty.

As with open reconstruction, some contraindications for laparoscopic bladder reconstruction include uncorrected coagulopathy, poor patient compliance, or the inability to perform clean intermittent catheterization. Relative contraindications for laparoscopic bladder reconstruction are short gut syndrome, severe inflammatory disease of the bowel or bladder (e.g., inflammatory bowel disease and bacterial cystitis), multiple prior open abdominal procedures, and prior radiation therapy with significant intra-abdominal adhesions.

Neither a history of previous abdominal surgery nor the use of peritoneal dialysis is a contraindication for laparoscopic bladder reconstruction. In addition, it is safe to perform laparoscopic surgery in patients with an existing ventriculoperitoneal shunt.[15,16]

PREOPERATIVE EVALUATION

Preoperative evaluation is similar to screening for open bladder reconstruction. All patients undergo complete urodynamic evaluation to assess bladder capacity, bladder compliance, and Valsalva leak point pressure. In addition, patients undergo a voiding cystourethrogram to assess for vesicoureteral reflux. In children with hydronephrosis, concominant ureteropelvic or ureterovesical junction obstruction must also be ruled out. Existing renal function is assessed with a serum creatinine and possibly a nuclear renal scan.

Patients must be prepared to perform clean intermittent catheterization. This may be done through a new catheterizable stoma, a newly reconstructed bladder neck, or the native urethra. It is not uncommon to require that the patient and family comply with a preoperative routine of regular catheterizations, which may be a few weeks or even a few months.

Other considerations include the possible need for bowel continence mechanisms. If an antegrade continence enema (ACE) is needed, it should ideally be accomplished at the same time.[17]

Laparoscopic Bladder Autoaugmentation

The concept of bladder autoaugmentation was first described in 1989 as an alternate method to increase capacity.[18] Since then, laparoscopic bladder autoaugmentation (LBAA) has been described through a transperitoneal and retroperitoneal approach.

The first transperitoneal laparoscopic bladder augmentation in a child was described in 1993.[19]

In 1998, a case series in seven children was reported by Braren and Bishop.

A 5 mm trocar was placed at the umbilicus. Two 5 mm working ports were placed in the left and right lower quadrants. Using direct visualization, both ports were placed lateral to the inferior epigastric vessels (Figure 60.1).

An elliptical incision was used to wedge out a segment of detrusor muscle while leaving the mucosa intact

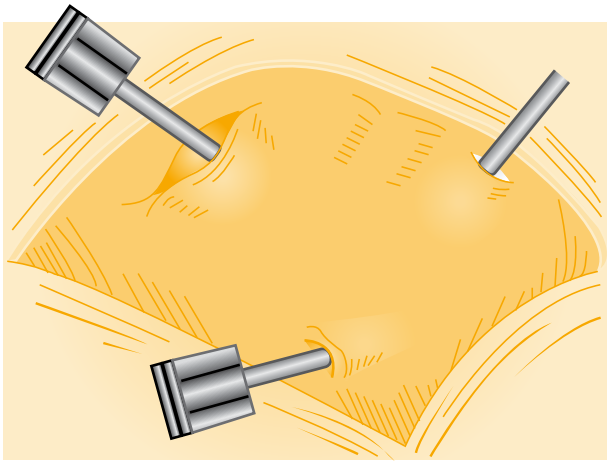

FIGURE 60.1 Three 5 mm trocars are placed. A camera port is located at the umbilicus. Two working ports are placed in the lower quadrants, lateral to the inferior epigastric vessels. (From Ehrlich RM, Gershman A. *Urology* 1993;42:175–8; Braren V, Bishop MR. *Urol Clin North Am* 1998;25:533–40. Reproduced with permission.)

(Figure 60.2). The bladder was filled with normal saline to assess the size of the created diverticulum and to assess for any leakage.

Operative time ranged from 55 to 93 minutes. The majority of patients were sent home the same day of the procedure.

Patients were followed between 10 months and 4 years. Bladder capacity increased from 55% to 95% of the original volume. Six patients achieved complete dryness.[20]

Extraperitoneal LBAA

Only one case of a preperitoneal LBAA has been reported. This was done in a 26-year-old female.

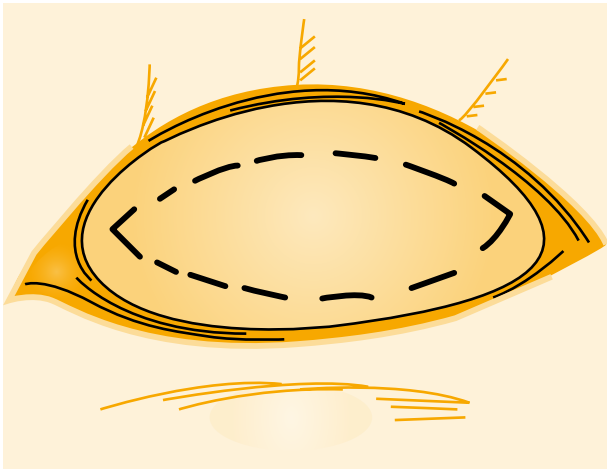

FIGURE 60.2 The detrusor muscle is divided in an elliptical fashion, leaving the underlying mucosa intact. (From Ehrlich RM, Gershman A. *Urology* 1993;42:175–8; Braren V, Bishop MR. *Urol Clin North Am* 1998;25:533–40. Reproduced with permission.)

The operation lasted 6.5 hours and had an estimated blood loss of 75 cc. The patient was discharged on postoperative day 2 with both catheters and ureteral stents in place. One catheter was left in place for 1 month before no leakage was confirmed on cystogram. Initially, the patient required intermittent self-catheterization and later voided by the Valsalva technique every 3 hours. At the 9-week and 6-month follow-ups, the patient was dry in the day and night.[21]

Laser LBAA

Poppas et al. then described a technique used in two pediatric patients. Both patients underwent a mechanical bowel preparation in preparation for a possible open enterocystoplasty if any difficulty with laparoscopy was encountered. Using an open technique, a 10 mm laparoscopic port was placed in an infraumbilical incision. Working ports (5 mm) were placed in the upper quadrants (one in the right and two in the left). A KTP 532 nm laser was used through a 600-micron fiber. This was done through a 5 mm port. The laser was used to incise the peritoneum overlying the bladder. The detrusor muscle was then mobilized bluntly, and the mucosa was easily visualized secondary to instilled methylene blue.

Each procedure lasted approximately 90 minutes. Initial results were favorable with no leakage and decreased detrusor peak pressure. However, at 4-month follow-up, there was urinary leakage between catheterizations and detrusor pressures greater than 40 cm H_2O. Ultimately, both patients underwent enterocystoplasty. At the time of that procedure, there was a thickened covering over the area of autoaugmentation. Pathology revealed mucosa with chronic inflammation but no muscular tissue.[22]

Although autoaugmentation is an ideal procedure for adaptation to a minimally invasive approach, the authors have no experience with the technique because long-term results have, in general, not been favorable. Nonetheless, this technique can be considered when the main goal is either improved compliance or decreased uninhibited contractions in a patient who already has adequate volume.

LAPAROSCOPIC ENTEROCYSTOPLASTY

Enterocystoplasty remains a commonly used technique for increasing bladder capacity. Classically, this is performed through an open laparotomy. First described in a canine model in 1888, it was then demonstrated in a clinical report in 1898.[23] As time has progressed, modifications have been made to improve operative technique and postoperative outcomes.

The first laparoscopic enterocystoplasty in an adult or child was a gastrocystoplasty that took place in 1994.[10] Three 12 mm ports were used. The camera port was placed through a supraumbilical incision. Two working ports were placed near the level of the umbilicus in the anterior axillary line. This access allowed manipulation within the pelvis, as well as the upper abdomen (Figure 60.3).

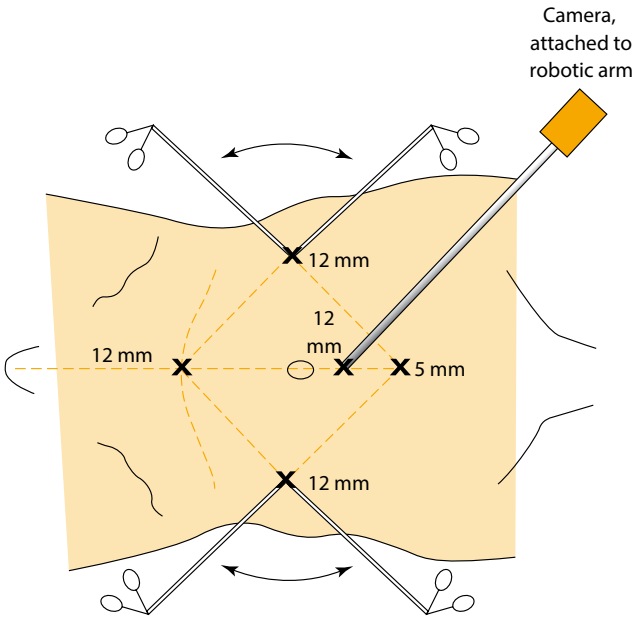

FIGURE 60.3 A camera is placed through the umbilicus. Two working ports are placed along the anterior axillary line. Positioning the working ports near the height of the umbilicus allows access into the upper abdomen and low into the pelvis. (From Docimo SG et al. *J Urol* 1995;154:1513–5; Meng MV et al. *J Urol* 2002;167:1386. Reproduced with permission.)

The dissection began by separating the bladder from the anterior abdominal wall. This dissection was taken caudally to the level of the urethra. Next, the greater omentum was separated and the right epiploic vessels were divided from the greater curvature. This division was performed using small clips close to the wall of the stomach.

A fourth 12 mm port was placed in the midepigastrium close to the pubic tubercle. A series of firings of an Endo-GIA stapler was used to resect a segment of the stomach (Figure 60.4). Stomach (20 cm) was isolated for the augmentation. This segment accounted for approximately one-third of the surface area of the stomach. The staple line of the stomach was oversewn with a 3-0 Vicryl suture in a running fashion. The bladder was then opened to the level of the urethra. The isolated gastric segment was sewn to the open bladder after the staple line had been removed. This started posteriorly and then moved anteriorly. Similar to the gastric segment, the anastomosis of the augmentation was completed with a 3-0 Vicryl suture in a running fashion. To assist in the anastomosis, an Endo-Stitch autosuturing device (Auto Suture Company, Norwalk, Connecticut) was used.

Due to incompetent bladder resistance, a modified Gittes bladder neck suspension was also performed. At the end of the procedure, a suprapubic catheter and an extravesical suction drain were placed. Operative time was close to 11 hours with no intraoperative complications.

Postoperatively, the patient was tolerating regular food on postoperative day 4. An external drain was required for 13 days until a urine leak sealed over. Because of social concerns, the patient was not discharged until the

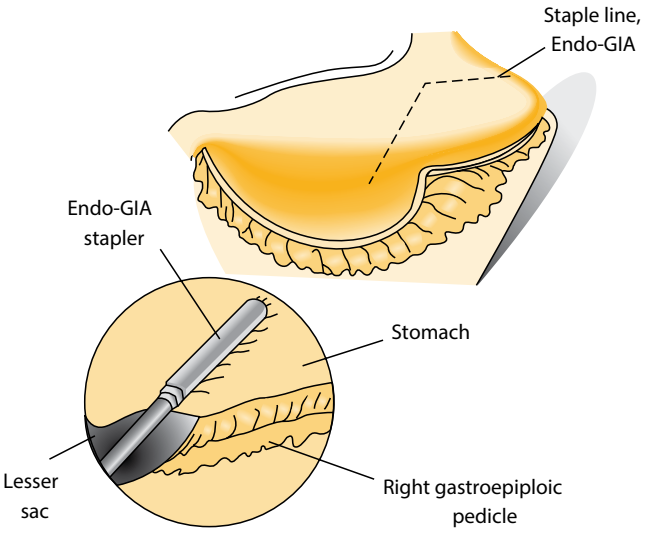

FIGURE 60.4 The gastric segment is isolated using multiple firing of an Endo-GIA stapler. (From Docimo SG et al. *J Urol* 1995;154:1513–5; Meng MV et al. *J Urol* 2002;167:1386. Reproduced with permission.)

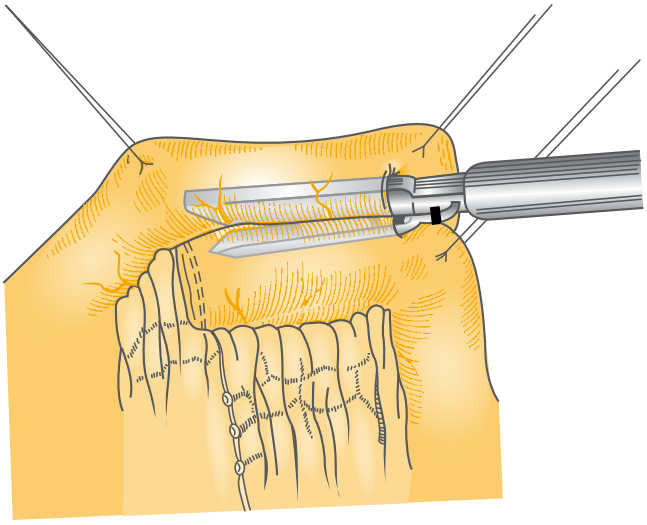

FIGURE 60.5 A gastrointestinal stapler can be used to divide the bowel segment. In addition, it may be used to perform the enteroenterostomy. (From Elliott SP et al. *Urology* 2002;59: 939–43; Hedican SP et al. *J Urol* 1999;161:267–70. Reproduced with permission.)

drain was removed. However, at the time of discharge the patient resumed normal activities.

The early outcomes from this case report were favorable. The bladder capacity doubled from 150 to 315 cc. The patient was dry on intermittent catheterization every 4 hours.[10]

Laparoscopic Ileal Augmentation

There are limited reports of ileal enterocystoplasty using a completely laparoscopic approach. Meng et al. described this technique in a 31-year-old paraplegic female. Five laparoscopic ports were used in a transperitoneal fashion. A gastrointestinal anastomotic stapler was used to divide the ileal segment and restore bowel continuity (Figure 60.5). The mesentery was incised using ultrasonic coagulating shears (Ethicon, Cincinnati, Ohio). Electrocautery was used to remove the stapled ends of the isolated segment and to open the segment on its antimesenteric side. Running 3-0 polyglactin sutures were used to configure the bowel into a U shape and to suture it to the opened bladder. At the end of the anastomosis, the bladder was irrigated and noted to have a watertight closure.

The operative time was 9 hours, and there were no intraoperative complications. Estimated blood loss was 100 mL. Postoperatively, the patient had a urethral catheter and an external Blake drain. On postoperative day 3, the patient resumed oral intake and had the Blake drain removed. Initial results showed an increase in bladder capacity from 85 to 400 mL. The bowel was returned to the peritoneum and ports replaced to reestablish a pneumoperitoneum.[24]

Although cases have been reported, the published outcomes are limited. A patient who had undergone the same procedure had follow-up at 8 months and had a bladder capacity of 550 mL and was continent in between catheterizations. But again, long-term outcomes data are limited.[25]

Small case series have been reported of laparoscopic enterocystoplasty using a combination of intracorporeal and extracorporeal techniques. The bowel segment used included ileum, sigmoid colon, and proximal colon.[26,27]

TECHNIQUE

A transperitoneal approach was used with four laparoscopic ports: a 12 mm port at the umbilicus, two working ports (5 or 12 mm) at the lateral edge of the rectus muscle at the level of the umbilicus, and a 5 mm port at the left anterior superior iliac spine (Figure 60.6). If sigmoid colon is used, an additional 10 mm port may be placed medial to the right anterior superior iliac spine.

The isolated bowel segment had to reach the bladder neck without tension and have a definitive arterial arcade in its mesentery. A laparoscopic camera is used to highlight the vasculature within the mesentery. Laparoscopic bowel clamps (5 mm) are placed accordingly. The umbilical port was widened 2 cm both circumferentially and inferiorly in the midline. The chosen segment was delivered outside of the abdomen. A total of 15–20 cm of bowel is needed. Using standard open methods, the segment was divided and the mesentery was closed (Figure 60.7). The bowel continuity was restored, keeping the isolated segment inferior to the mesentery of the remaining bowel. To minimize edema, the bowel segment was placed back into the peritoneum before continuing further manipulation.

The isolated bowel segment was divided on its antimesenteric side and irrigated with saline. Small bowel and sigmoid were refashioned in a U shape using 2-0 Vicryl in a side-to-side fashion (Figure 60.8). If a catheterizable stoma is created, the terminal ileum is narrowed over a 16 Fr red rubber catheter using a gastrointestinal stapler (GIA stapler, U.S. Surgical Corporation, Norwalk, Connecticut). This red rubber catheter was secured to the terminal end

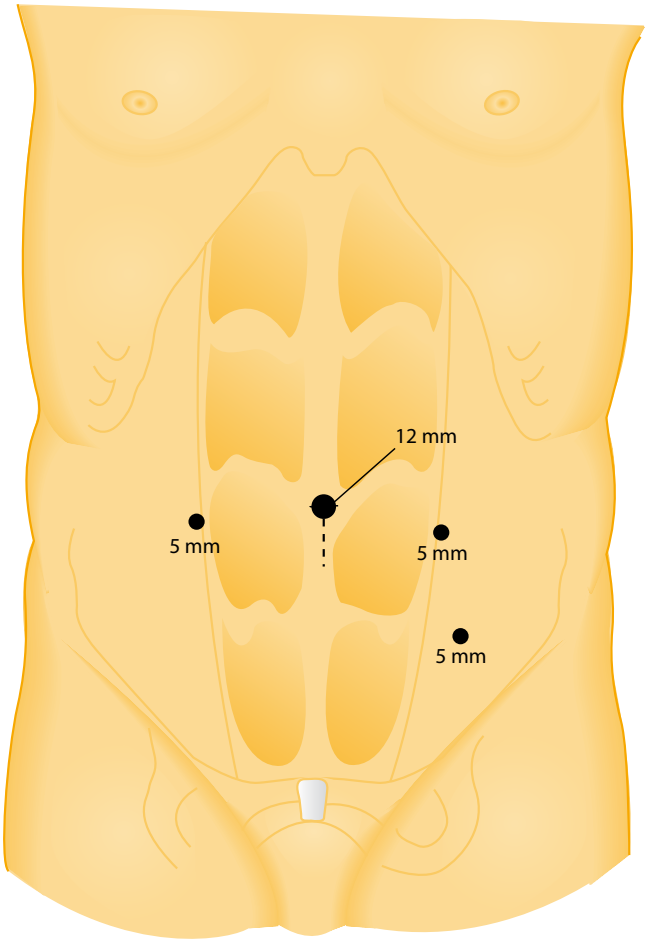

FIGURE 60.6 Laparoscopic enterocystoplasty port placement: a 12 mm port at the umbilicus, a 5 mm port next to the anterior superior iliac spine, and two 5 mm ports on the lateral edge of the rectus muscle at the level of the umbilicus. (From Gill IS et al. *Urology* 2000;55:178–81; Hedican SP et al. *J Urol* 1999;161:267–70. Reproduced with permission.)

of the ileum, which assisted in intracorporeal manipulation and delivery to the umbilicus. The bowel was returned to the peritoneum and ports replaced to reestablish a pneumoperitoneum.

To facilitate the enterovesical anastomosis, the bladder was filled with saline and the patient placed in the Trendelenberg position. The peritoneum was incised from the medial border of the left medial umbilical ligament to the right medial umbilical ligament. A large cystotomy was created by making a curvilinear incision that allowed maximal disruption of the detrusor muscle (Figure 60.9). The anatomosis to the bladder started posteriorly because starting at the anterior can inhibit visualization for the remaining anastomosis. A 5 mm laparoscopic needle driver was used to perform freehand intracorporeal suturing and knot tying. An assistant followed with a 5 mm grasper. An Endo-Stitch was used to facilitate this step (Figure 60.9).

If a catheterizable stoma is required, the right colon and terminal ileum are utilized. These segments can be isolated after incising the peritoneum laterally and then mobilizing the segments through an extending umbilical incision. In order to manipulate the laparoscopic equipment in the

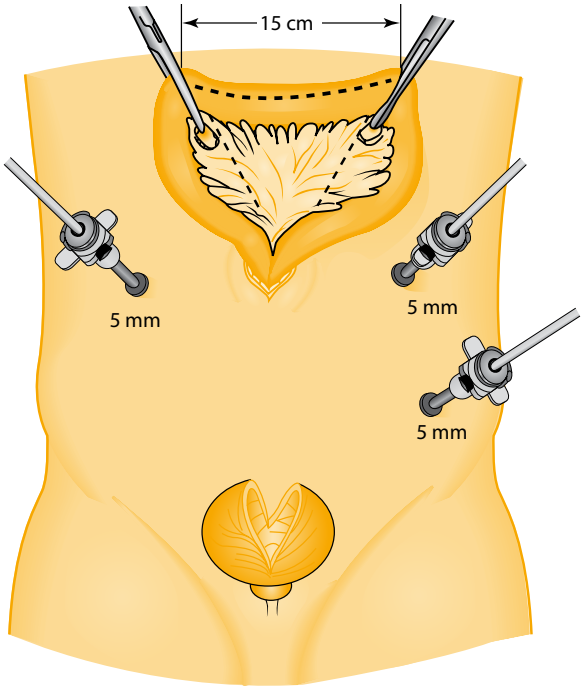

FIGURE 60.7 The umbilical incision is extended 2 cm circumferentially and inferiorly. Through this incision, the isolated bowel segment is delivered for resection and reanastomosis. (From Gill IS et al. *Urology* 2000;55:178–81; Hedican SP et al. *J Urol* 1999;161:267–70. Reproduced with permission.)

lower ports, it is important that the patient is positioned in low lithotomy.[26]

RESULTS

In the series by Gill et al., all patients had two Jackson–Pratt (JP) drains left in place. These were placed through the preexisting port sites. Operating time ranged from 5.3 to 8 hours. Intracorporeal suturing took between 1.7 and 2.1

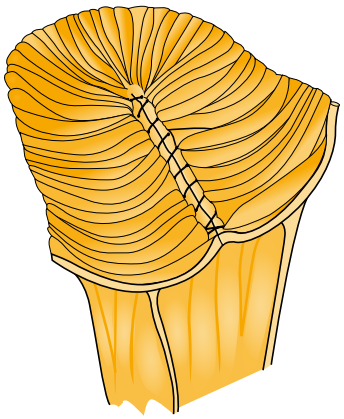

FIGURE 60.8 The bowel segment is refashioned in a U shape before performing the anastomosis. (From Rackley RR, Abdelmalak JB. *Urol Clin North Am* 2001;28:663–70; Gill IS et al. *Urology* 2000;55:178–81. Reproduced with permission.)

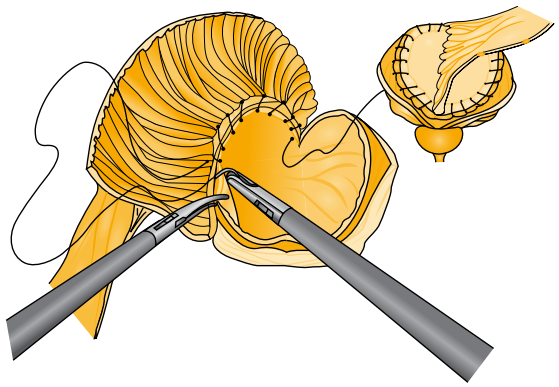

FIGURE 60.9 The enterovesical anastomosis is performed using a laparoscopic needle driver. Starting posteriorly, a continuous, full-thickness suture is used. (From Gill IS et al. *Urology* 2000;55:178–81; Hedican SP et al. *J Urol* 1999;161:267–70. Reproduced with permission.)

hours. Patients were discharged between postoperative days 2 and 5. A urethral catheter was left in place for 1 month and removed after a cystogram confirmed no leakage.[27]

The series by Rackley and Abdelmalak had an average operative time of 7 hours. The average time for laparoscopic suturing was 2.4 hours. The average blood loss was 175 mL. The majority of patients resumed oral intake 24 hours postoperatively. The average date of discharge was 5.7 days. The only complication noted was a rectus sheath hematoma secondary to port placement. This was recognized and corrected laparoscopically.[26]

Laparoscopic-Assisted Bladder Reconstruction

The most easily available and performed technique in minimally invasive reconstruction is the laparoscopic-assisted approach. The biggest concerns with a purely laparoscopic approach are the technical challenges of bowel manipulation, irrigation, and anastomosis. This can be intricate and time-consuming. In addition to time, reconstructive urologists are concerned about the technical ability to match the outcomes of open procedures. The goal of laparoscopic-assisted surgery is to combine the morbidity and cosmetic benefits of laparoscopy with the technical precision of open reconstruction.[28]

By using laparoscopy, the required bowel segments can be isolated and mobilized quickly with small access ports. Once the bowel segment is freed, the ureter or stomach harvested, and the omentum mobilized, the more precise aspects of the surgery can be performed through a small lower abdominal incision. If a bladder augmentation is planned without any bladder neck reconstruction, ureteral reimplantation, or continent stoma, this can often be done simply with a lower abdominal incision, and no laparoscopy is required.

The biggest benefit of laparoscopy is the ability to quickly mobilize the necessary bowel segments without the upper aspect of a large abdominal incision. Many of the pediatric patients requiring bladder reconstruction have an underlying neurologic disorder, such as myelomeningocele. These patients often have an abnormally rotated cecum and appendix with position in the right upper quadrant.[29] Although challenging to reach through a lower abdominal incision, the high cecum can easily be reached with laparoscopy. Patients with spina bifida may have severe lordosis, which can inhibit the mobilization of the cecum.[30] In addition, laparoscopy can easily allow lysis of adhesions that may have developed because of prior surgeries or long-term ventriculoperitoneal shunts. The presence of a shunt is not a contraindication to laparoscopic surgery.[16]

Once the needed segments are harvested, a lower midline or Pfannensteil incision is used to mobilize the bladder and bladder neck and to assemble the anastomosis. The lower abdominal incision may incorporate one of the lower abdominal ports as well (Figure 60.10).

The technique allows dissection similar to that of the open technique, with smaller incisions and lower morbidity.[10,31]

Using laparoscopic assistance to create an appendicovesicostomy was first described in 1993.[31] Since that time, there have been other reports of successful laparoscopic bladder reconstruction with creation of continent stomas.[28,30,32,33] The only large reported series is from Docimo and colleagues.[32]

TECHNIQUE

Preoperatively, the patient undergoes a mechanical and antibiotic bowel preparation if considered indicated.[34,35] Intraoperatively, the patient is positioned supine. If a concominant nephrectomy or ureterocystoplasty is

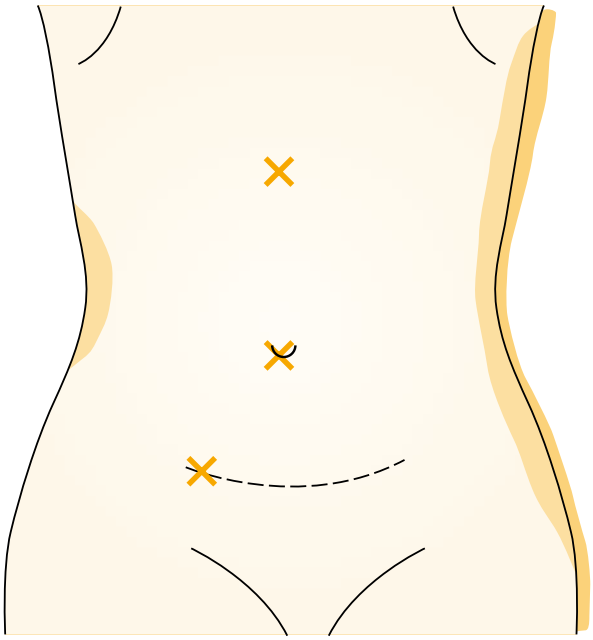

FIGURE 60.10 After harvesting the necessary bowel segments, the lower working port can be incorporated into a Pfannenstiel incision. (From Hedican SP et al. *J Urol* 1999;161:267–70; Brown SF. *J Iowa Med Soc* 1975;65:101–4. Reproduced with permission.)

anticipated, the patient may be positioned in a modified flank position. The patient is padded with foam and gel pads to protect any pressure points. In addition, the patient is secured to the table to allow repositioning with steep Trendelenberg and lateral rotation as needed.

Intravenous antibiotics are given to cover gram-positive and gram-negative bacteria. After induction of general anesthesia, a nasogastric tube is placed. If possible, an epidural catheter is also placed.

The first step is obtaining peritoneal access. If a concealed umbilical stoma is anticipated, a U-shaped flap is created on the lower umbilicus.[11] For the purposes of achieving a straight stoma, the fascia inferior to the umbilicus is opened and the peritoneum entered under direct vision. A radially dilating trocar sleeve is inserted into the peritoneum, and dilated using the trocar insert. This should be 10 or 12 mm in size to allow easy passage of the stomal segment without creating too large a defect, which would risk parastomal herniation.

Placement of the working ports depends on the type of repair planned and the bowel segments needed. Most commonly, two working ports are used. A 3 or 5 mm epigastric port is placed between the umbilicus and the xyphoid. An additional port in the lower abdomen can be of variable size because it will be incorporated into the abdominal incision (Figure 60.11). If an additional stoma is created (i.e., ACE), another U-shaped incision is made in the right lower quadrant and a 10 mm port placed at this site.

Laparoscopy is for bowel manipulation, lysis of adhesions, performing nephrectomies, harvesting ureter, and harvesting omentum.

If appendix is needed, the right colon is mobilized until the appendix can reach the lower abdominal incision. Through the open incision, the appendix can be divided from the cecum. An alternative is to isolate and divide the appendix using an Endo-GIA stapler. If this approach is chosen, care must be taken to avoid disruption of the mesoappendix (Figure 60.12). If laparoscopic examination reveals an appendix in the deep pelvis, easily accessed through a Pfannensteil incision, further laparoscopic dissection is not necessary.

FIGURE 60.11 After incorporating the lower port into a Pfannenstiel incision, the visible scars are minimized. Here the umbilical port site was used for the continent stoma, and the lower port healed within the Pfannenstiel scar. (From Chung SY et al. *J Urol* 2004;171:372–5; Strand WR et al. *Urology* 1997;49:272–5. Reproduced with permission.)

FIGURE 60.12 The majority of bowel manipulation can be done through a lower midline or Pfannenstiel incision. (From Chung SY et al. *J Urol* 2004;171:372–5; Strand WR et al. *Urology* 1997;49:272–5. Reproduced with permission.)

After the laparoscopic portion of the procedure is completed, a 4–5 cm Pfannensteil incision is made. This can incorporate the lower working port. To minimize bowel manipulation, the peritoneum is left intact and any bladder work is completed first. This may include bladder neck division or reconstruction, ureteral reimplantation, and cystolitholapaxy. The next step is opening the bladder, implanting the continent stomal segment, and creating the anastomosis to the augment. All stomas are matured to the skin, and any redundancy is addressed to allow easy catheterization. The bladder stoma is spatulated dorsally and then secured to the U-shaped flap. This helps conceal the stoma and reduce the chance of stenosis. The entry site of the stoma to the bladder is secured to the anterior abdominal wall to decrease the likelihood of eventual tortuosity and difficulty with catheterization.

Postoperatively, most patients are left with a nasogastric tube, a suprapubic tube, and a 10 Fr stomal catheter. Drains are rarely used. The stomal catheter is secured to the skin with the balloon deflated to avoid excess tension on the continence mechanism.

RESULTS

Laparoscopic-assisted bladder reconstruction allows patients to resume a normal diet faster and leave the hospital earlier. These outcomes exist without an increase in operative time or perioperative complications.[28,36]

In 2004, a series of 31 patients with a mean age of 14 years was reported. Twenty-nine of 31 patients had at least one stoma created. Ten patients had both a Mitrofanoff and an ACE stoma created. Nineteen patients had

additional procedures performed (e.g., fascial sling, bladder neck reconstruction, revision of epispadias, ureteral reimplantation, and revision of orchidopexy).

The mean hospital stay was 6 days. The mean follow-up was 32 months. Of all stomas, 94.9% were continent of either urine or stool and easy to catheterize. Improved compliance and capacity were maintained at last follow-up. There were no late bowel obstructions or other sequelae of problematic adhesion formation. Stomal stenosis occurred in 5.1%, and 7.7% required stomal revision secondary to incontinence or difficulty with catheterization. Minor procedures were required in 25.6% of stomas.

Complications occurred in five patients. This included the ileus, a partial small bowel obstruction, a delayed bladder perforation, deep vein thrombosis, and a wound infection.[32]

Robotic-Assisted Lower Tract Reconstruction

Robotic surgery offers several technical advantages over traditional laparoscopic surgery, such as a three-dimensional stable visual field, tremor reduction, and elimination of the fulcrum effect. However, the greatest advantage of robotic technology in reconstructive surgery is the ability to perform wristed intracorporeal suturing. Multiple studies have demonstrated faster speed, greater precision, improved dexterity, and a shorter learning curve of robotic suturing over conventional laparoscopic suturing.[37–41] In recent years, these advantages have been increasingly applied to laparoscopic lower urinary tract reconstruction in children.

Robotic Appendicovesicostomy

In 2004, Pedraza et al. reported the first case of a robotic-assisted laparoscopic appendicovesicostomy in a 7-year-old boy with posterior urethral valves, incomplete bladder emptying, and recurrent urinary tract infections.[42] The procedure took 6 hours, and the authors felt that the greatest advantage of the robotic approach was the ease in creation of the appendicovesical anastomosis. In 2007, Storm et al. reported three cases of robotic-assisted appendicovesicostomy in three patients aged 9, 17, and 45 years, with a follow-up range of 1–8 months.[43] Their mean operative time was 301 minutes. The next two cases of robotic appendicovesicostomy were not reported until 2008, both in combination with ACE procedures employing a split-appendix technique.[44,45]

In 2009, Nguyen et al. published the largest series to date of 10 cases of robotic-assisted laparoscopic appendicovesicostomy with a median follow-up of 14.2 months.[46] The original diagnoses of the patients included posterior urethral valves, spina bifida, spinal cord injury, and nonneurogenic neurogenic bladder. The mean operative time was 323 minutes but ranged from 181 to 507 minutes. One open conversion occurred secondary to inadequate appendiceal length. The stomal incontinence rate was a 20% complication rate. The overall complication rate was 50%, which included stomal incontinence, postoperative pulmonary distress (in a case that took 7 hours, 22 minutes), the need for open conversion, urine leakage, and pyonephrosis. The median length of stay was 5 days.

In this series, the authors did emphasize the significant learning curve associated with this procedure, as operative times decreased with greater experience. They reported that hitching the bladder to the anterior abdominal wall (prior to the appendicovesical anastomosis), adequate cecal mobilization, and measurement of the appendix to ensure adequate length were all useful maneuvers to reduce operative time.

Robotic Bladder Neck Sling Placement and Bladder Neck Reconstruction

Inadequate bladder outlet resistance is a common cause of urinary incontinence in children born with myelomeningocele. Until recently, bladder neck procedures in these children, such as sling placement or bladder neck reconstruction, have not been performed in a laparoscopic fashion secondary to technical limitations. However, the technical advantages of a robotic approach have allowed these complicated procedures to be accomplished laparoscopically.

Although published experiences are limited, Bagrodia and Gargollo reported four cases of patients with myelomeningocele managed with robotic-assisted laparoscopic bladder neck sling placement, Leadbetter–Mitchell bladder neck reconstruction, and appendicovesicostomy.[47] One was converted to an open approach secondary to adhesions related to a ventriculoperitoneal shunt. Although the length of follow was not specifically listed, urinary continence was reported as 100%. The mean operative time of 7 hours, 45 minutes certainly reflects the technical complexity of the procedure, but this report serves as proof of principle that bladder neck sling placement and bladder neck reconstruction can be successfully performed in a robotic-assisted laparoscopic fashion.

Robotic Bladder Augmentation

Literature regarding complete intracorporeal laparoscopic bladder augmentation is limited. In 2008, Gundeti et al. reported the first case of a complete intracorporeal robotic-assisted laparoscopic augmentation ileocystoplasty and appendicovesicostomy in a 10-year-old girl with myelomeningocele.[48] They utilized a nonreconfigured 20 cm ileal patch and performed the ileoileal anastomosis in a hand-sewn fashion. The procedure took 10 hours. At 6 weeks' follow-up, the authors reported complete continence.

In 2010, Gundeti et al. reported a series of five patients with myelomeningocele and incontinence who underwent robotic-assisted laparoscopic bladder augmentation with ileum.[49] Four of the five patients also underwent appendicovesicostomy creation. A sixth patient required open conversion secondary to intraoperative adhesions and difficulty achieving pneumoperitoneum. The mean operative time was 8.4 hours (range 6–11 hours). Similar to their initial case report, the bowel patch was not reconfigured. Postoperative complications included deep venous

thrombosis in one patient, knee parasthesia and wound infection in one patient, and paralytic ileus in one patient. Three of four patients who underwent appendicovesicostomy required stomal revision. Although continence was reported as 100%, postoperative bladder capacity ranged from 150 to 450 mL, with two patients having a maximal daytime bladder capacity of 200 mL. Although this series demonstrates the feasibility of the technically challenging procedure, whether there are specific benefits and an acceptable postoperative bladder capacity remains controversial.

CONCLUSIONS

Minimally invasive bladder reconstruction has become our standard approach. The outcomes match or exceed those of open operations, with recovery and cosmetic benefits. Long-term benefits of decreased intra-abdominal adhesions will be hard to measure, but may be the most important reason to continue to pursue these techniques. The ability of reconstructive surgeons to achieve consistent results depends on the precision of reconstructive techniques. Robotic-assisted approaches to lower urinary tract reconstruction are becoming more widespread and should be considered the state of the art. One thing that is certain: In this era, there is no need for a large abdominal incision in the majority of children who require bladder reconstruction.

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CHAPTER
61

Genitourinary Rhabdomyosarcoma and Other Bladder Tumors

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INTRODUCTION

Accounting for 4.5% of all childhood cancers, rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in children under the age of 15 and has an incidence of 4.5 cases per million children (0–19 years old) per year in the United States between 1975 and 2005.[1,2] After neuroblastoma and Wilms' tumor, it is the third most common childhood extracranial solid tumor, and accounts for 60%[3] of all childhood sarcomas and 10%–15% of all solid pediatric tumors. Approximately 26% of these tumors arise from the genitourinary (GU) tract (10% from bladder or prostate) and another 16% from pelvic or retroperitoneal sites (paratesticular region, perineum, vulva, vagina, and uterus).[4–7] Since its discovery by Weber in 1854, extensive studies of the clinical and pathologic features of RMS have resulted in the development of uniform diagnostic criteria and prognostically relevant staging systems.[8]

A member of the group of small, round blue cell tumors (including neuroblastoma, lymphoma, and the primitive neuroectodermal tumors), RMS is a sarcoma demonstrating evidence of skeletal muscle differentiation. The fact that it can occur outside sites where skeletal muscle is found suggests that it is a tumor of primitive mesenchymal skeletal muscle differentiation.[9]

Histopathological variants of RMS (embryonal, botryoid, and alveolar) pursue different biologic courses. Embryonal RMS (eRMS) tends to occur in the head and neck and GU system, and the majority of patients survive beyond 5 years. In contrast, with few patients surviving beyond 5 years, alveolar RMS (aRMS) often presents with tumors in the extremities and early metastasis.[10]

The cure rate for patients with RMS improved significantly in the latter part of the last century from an estimated 25% in 1970 to 70% in 1995.[9,126,127] This improvement is credited to the use of increasingly effective multimodal, risk-adapted therapy; refinement in tumor grouping; better diagnostic imaging; and better supportive care, which have been developed through multiple international collaboratives, including the International Rhabdomyosarcoma Study Group (IRSG) trials IRS I–IV, which have transitioned to the Soft Tissue Sarcoma Committee of the Children's Oncology Group (COG), the Cooperative Soft Tissue Sarcoma Group (CWS), and the European Soft Tissue Sarcoma Study Group. Emerging information on the numerical and structural abnormalities of tumor cell chromosomes and the development of probes to identify molecular genetic lesions has improved diagnostic methods and afforded new insights into tumor pathogenesis, allowing for improved risk stratification and paving the way for advances in risk-based therapy.

EPIDEMIOLOGY

Nearly three-quarters of GU RMS cases are diagnosed before the age of 5 years, with a 3.3:1 male predominance. RMS has two large peaks of incidence: the first, accounting for more than half of the cases, occurs in the first decade and is mainly eRMS or botryoid RMS (bRMS); the second occurs during adolescence and is more frequently aRMS.[11,12]

Associated Syndromes

RMS may be associated with congenital anomalies, most commonly affecting the GU system, but also the central nervous system. Interestingly, patients with RMS are noted to have fewer musculoskeletal anomalies.[3]

Occurring in 0.5% of patients enrolled in IRS IV, neurofibromatosis is the most common syndrome in which RMS has been described. Among the five RMS patients with neurofibromatosis, three relapsed, and two of whom died of progressive disease. Because of the progressive nature of RMS in patients with neurofibromatosis, it is recommended that they be treated with intensive contemporary therapy protocols.[13]

Costello syndrome (HRAS mutation) is associated with an increased risk of solid tumors, the most common of which is RMS. Gripp et al. recommended a screening protocol of abdominal or pelvic ultrasound every 3–6 months up to 8–10 years for RMS and neuroblastoma in patients with Costello syndrome.[14]

Other congenital syndromes in which RMS has been reported include multiple endocrine neoplasia 2A, Gorlin's basal cell nevus, Rubenstein–Taybi, trisomy 21, Beckwith–Wiedemann (BWS), Li–Fraumeni, Noonan, Roberts,

Dubowitz, Nijmegen breakage, multiple lentigines, and constitutional mismatch repair deficiency syndromes.[15,16] While Wilms' tumor is the most common malignancy associated with BWS, in the first 7 years of life, RMS, adrenocortical carcinoma, and hepatoblastoma may also be seen.

Li–Fraumeni syndrome is associated with a known p53 mutation with autosomal dominant transmission. These patients are predisposed to multiple tumors, which often retain a normal p53 allele, suggesting that an alternate additional tumorgenic mechanism is involved in p53 inactivation. Malkin et al. evaluated two patients with multiple tumors in the presence of Li–Fraumeni syndrome who had a heterozygous germline p53 mutation. Tumors that they developed that maintained p53 heterozygosity were noted on immunostaining to contain the DNA tumor virus SV40. The authors postulate that p53 inactivation by viral proteins may contribute to tumor formation in these genetically susceptible patients.[17–19]

Environment

Environmental factors associated with RMS include ionizing radiation and alkylating agents. The increased risk of secondary malignancies in those patients with neurofibromatosis and Li–Fraumeni syndromes after treatment with alkylating agents and radiotherapy (RT) for RMS draws a link between the likely dual causation of malignancy by genetics and the environment. It is therefore particularly desirable to limit the use of alkylating agents and RT in these populations.[3]

GENETICS

Somatically acquired genetic changes underlie all forms of cancer, and the chromosomes of RMS contain both numerical and structural abnormalities.[20–22] Advances in the molecular and cellular biology of RMS have further elucidated the pathogenesis of this tumor and will aid in its diagnosis, staging, management, and risk stratification.

RMS appears to develop from a derangement in the final steps of myogenic differentiation. Genes of the *MyoD* family are crucial in the early differentiation of skeletal muscle precursors.[23,24] These genes express DNA binding proteins that facilitate the production of myogenic proteins, such as desmin, creatine kinase, and myosin. *MyoD* expression is higher in RMS cells. Activation of p38 MAP kinase, which is required for muscle differentiation, is absent in RMS cells.[25] Failing to differentiate completely, RMS cells continue to produce forms of actin seen only transiently in normal-developing skeletal muscle.[26] *MyoD1*, a myogenic regulatory protein, maps on chromosome 11p15.4 and is expressed during skeletal muscle development. Myogenin is a myogenic regulatory protein whose expression determines differentiation of primitive mesenchymal cells into skeletal muscle. It is regulated by pathways involving p38, calcium–calmodulin-dependent protein kinase (CaMK) or calcineurin, and its expression may be downregulated with terminal differentiation. The activation of myogenin by CaMK and calcineurin pathways fails in RMS cell lines.[27]

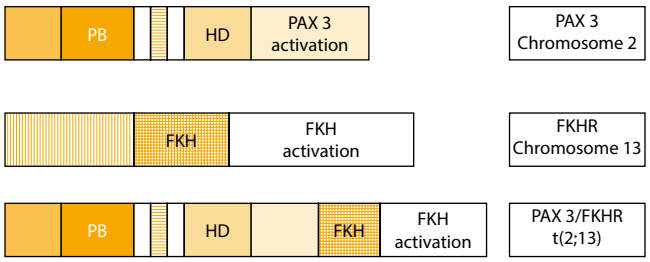

FIGURE 61.1 Structure of PAX3 on chromosome 2, the FKHR on chromosome 13, and the fusion product PAX-FKHR of the t(2;13) in aRMS. PB, paired box; HD, homeodomain; FKH, forkhead.

aRMS may be distinguished from eRMS and other tumors on the basis of genetic abnormalities. Cytogenetic analysis of aRMS revealed a chromosome 2;13 translocation unique to this tumor in 70%–80% of cases (Figure 61.1).[28–32] 1;13 translocations have also been identified.[30,33,34] These fusions result in expression of chimeric transcription factor PAX3-FKHR t(2;13)(q35;q14), or the less frequent PAX7-FKHR t(1;13)(p36;q14).

The presumed function of PAX3 is that of transcriptional regulation strictly during embryogenesis, important in the development of mesenchymal precursors.[35] A full-length cDNA of the wild-type chromosome 13 gene was cloned and found to be a novel widely expressed member of the forkhead transcription factor family.[36,37] A conserved DNA binding motif termed the "forkhead" domain characterizes this family. Based on homology to this family, the chromosome 13 gene was named FKHR for "forkhead in rhabdomyosarcoma."[36] These combined findings indicate that t(2;13) results in a chimeric transcript composed of 5′ PAX3 and 3′ FKHR exons (Figure 61.1). In the PAX3-FKHR fusion, the PAX3 gene within band 2q35 is fused with the FKHR gene within band 13q14. Both of the PAX3 DNA binding regions (the paired box and the homeodomain) are retained in the fusion gene, whereas the carboxyl-terminal sequences are replaced by the bisected forkhead DNA binding sequences of FKHR.[8,38] In PAX7-FKHR fusions, a chromosome 1 locus encoding PAX7,[37] another member of the paired box family, is rearranged and fused to FKHR in the t(1;13) conscript consisting of 5′ PAX7 and 3′ FKHR regions, which is very similar structurally to the 5′ PAX3-3′ FKHR transcript formed by the t(2;13) translocation.[39,40]

Assays of expression during embryogenesis demonstrate that PAX3 and PAX7 are expressed with specific temporal and spatial patterns in early skeletal muscle progenitors, the presumed origin of aRMS.[41,42] PAX3-FKHR and PAX7-FKHR fusion proteins affect the cellular activities of growth, myogenic differentiation, and apoptosis, and enhance cellular proliferation and invasion.[31,32,43,44] PAX3-FKHR results in genetic overexpression, while PAX7-FKHR is associated with gene amplification.[1]

PAX3-FKHR is capable of inducing myogenin and MyoD. It is also associated with upregulation of *Six1*, *Slug*, and *Igfbp5*, which are all genes associated with muscle development and noted to be upregulated in aRMS.[45] Insulin-like growth factor (IGF1) has an important role in muscle development and in the etiology of aRMS.

PAX3-FKHR has been shown to transactivate the IGF1 receptor gene (IGF1R) promoter in sarcoma cell lines with a higher potency than PAX3.[46]

Sorensen et al. determined the PAX3/PAX7-FKHR fusion status in 171 patients enrolled in IRS IV, identifying PAX3-FKHR and PAX7-FKHR fusions in 55% and 22% of the 78 patients with alveolar histology, respectively, and none with other than aRMS. Fusion status was a prognosticator for metastatic but not local disease, with an estimated 4-year overall survival (OS) of 75% with PAX7-FKHR versus 8% with PAX3-FKHR. Failure, death, and bone marrow involvement were all significantly increased on multivariate analysis in patients with metastatic disease harboring PAX3-FKHR compared with PAX7-FKHR.[47] This corroborated results by Anderson et al., who had previously evaluated 91 RMS tumors. Thirty-seven patients had PAX3-FKHR, 8 had PAX7-FKHR, and 46 had neither. The authors found a statistically significant association between PAX3-FKHR and higher-stage disease and its absence and lower-stage disease ($p = 0.06$ when grouping stages 1 and 2 and stages 3 and 4). PAX7-FKHR transcript numbers were too small to reach statistical significance, but stage results were similar to those of the fusion-negative group. PAX3-FKHR occurred in statistically significantly older children than the other two groups, and translocation status was not associated with disease site. Among 66 patients with nonmetastatic disease, OS and event-free survival (EFS) were significantly worse in the PAX3-FKHR group.[48] Collins et al. found that compared with PAX7-FKHR, PAX3-FKHR RMS demonstrated greater cell cycle dysregulation related to both increased cell proliferation and apoptosis and concluded that this contributes to the poorer prognosis in the PAX3-FKHR group.[49] Stegmaier et al. evaluated PAX-FKHR fusion status for the CWS from 1996 to 2004 and confirmed earlier findings that PAX3-FKHR was more common than PAX7-FKHR fusion (60% vs. 24%, $n = 121$), and that in metastatic aRMS, the fusion-negative cohort showed a more favorable outcome than the fusion-positive one. The PAX3-FKHR group demonstrated adverse prognostic factors in age and stage distribution despite no differences in survival compared with those with the PAX7-FKHR fusion.[50]

Davicioni et al. molecularly characterized 160 RMS (70 aRMS, 78 eRMS, and 12 non-RMS) samples from patients enrolled in IRS IV and V. eRMS did not demonstrate PAX-FKHR translocation but had recurrent allelic imbalances, such as loss of heterozygosity (LOH) 11p15.5.[51] Chromosome 11 LOH is also seen in Wilms' tumor and hepatoblastoma, and alterations in this chromosome region are also noted in BWS.[52] A five-gene classifier (TFAP2β, CDH3, CNR1, MYOG, and CDH15) was useful in differentiating fusion-positive aRMS, fusion-negative aRMS, and undifferentiated sarcoma. Those genes that were overexpressed in PAX-FKHR-negative tumors were overrepresented by genetic loci on chromosome 8 to include an increased frequency of LOH 8q.[51]

Williamson et al. characterized subgroups of fusion-negative aRMS, fusion-positive aRMS, and eRMS for 101 RMS patients treated on European Soft Tissue Sarcoma Study Group protocols MMT 89, 95, IV 89/91, and 98. Fusion-negative aRMS was similar to eRMS with statistically significantly improved OS and EFS compared with fusion-positive aRMS, with the relative risk of death with fusion-positive aRMS of 2.5. Identifying few genes consistently distinguishing fusion-negative aRMS from eRMS, the authors identified that metagene expression is distinct between fusion-positive and fusion-negative aRMS, but not between fusion-negative aRMS and eRMS, and genetic expression analysis correctly characterized fusion-positive aRMS and eRMS in 99% and 95% of cases, respectively, while 100% of fusion-negative aRMS were genetically classified as eRMS. Additionally, chromosome 8 gains had a similar high frequency in fusion-negative aRMS and eRMS, but not in fusion-positive aRMS.[53] Fusion-negative aRMS appears to behave clinically more closely to eRMS than to fusion-positive aRMS, and on genetic mapping, is a heterogeneous group that overlaps with eRMS.[1,51,53,54] Davicioni et al. further evaluated the genetic expression of RMS with a 34-metagene analysis and identified tertiles whose clinical outcome correlates with COG clinical risk stratification.[55] Ongoing research involves the validation of these gene signatures for clinical application as a potential prognosticator for risk stratification to determine treatment protocols.[56]

Genetic Therapy

Potential gene targets for novel treatment options in RMS refractory to current regimens include receptors and growth factors (such as IGF1R, IGF2, c-Met, PDGFR, C-Kit, and FGFR1), intracellular signaling molecules (such as mTor), cell cycle (CDK4/CDK6), apoptosis (such as p53, Bcl-2, and TRAIL), angiogenesis (vascular endothelial growth factor [VEGF] and VEGF receptor [VEGFR]) and cancer-specific fusion proteins (PAX3-FKHR). Many of these therapies are under evaluation in current clinical trials.[57–60] MYCN gene amplification, associated with aRMS, is a direct downstream target of the PAX3-FKHR fusion protein and has been identified by Tonelli et al. as a potential tumor-specific therapeutic target utilizing gene therapy in the treatment of RMS.[61–63]

PATHOLOGY

The significant difference in survival between eRMS and aRMS makes accurate diagnosis imperative in order to predict the biological course of the disease and initiate appropriate therapy.

Embryonal RMS

eRMS represents the most common GU RMS variant. These tumors have variable amounts of spindle and primitive round cells, which may be either tightly packed or loosely dispersed in a myxoid background. The rhabdomyoblast, the more mature embryonal component, is characterized by bright eosinophilic cytoplasm and may appear in a variety of unusual shapes, termed "tadpole," "racquet," or "strap" cells.[10,64] Cross-striations are seen in 50%–60% of cases. These tumors rarely metastasize and respond well to current therapy. On fine-needle aspirate (FNA), the embryonal subtype is suggested in specimens

with large tissue fragments containing abundant eosinophilic material and small, tightly packed cells with oval nuclei.[65,66] eRMS stains positively for myoglobin, desmin, and vimentin. Classic eRMS with a polypoid growth pattern was associated with a more favorable prognosis than a diffuse intramural (endophytic) growth pattern in 65 cases of bladder and vaginal RMS (92% vs. 68% 10-year survival, $p = 0.02$).[67]

Botryoid Embryonal RMS

Botryoid eRMS tends to be a polypoid lesion filling a hollow viscus (vagina or bladder).[11] The International Classification of Rhadomyosarcoma (ICR) criterion for diagnosis of botryoid eRMS requires demonstration of a cambium (condensed layer of rhabdomyoblasts) tumor layer underlying an intact epithelium in at least one microscopic field (Figure 61.2). This microscopic criterion supersedes any gross demonstration of a "grapelike" tumor mass. An extensive degree of rhabdomyoblastic differentiation can be evident both in the cambium layer and elsewhere in the tumor. The importance of diagnosing this subtype is evident given its superior prognosis with a 95% 5-year survival. There remains debate as to whether bRMS is a distinct entity or a variant of eRMS, and biologic studies have not demonstrated a molecular distinction.[68]

Spindle Cell Embryonal RMS

The spindle cell variant of RMS also demonstrates a superior prognosis with an 88% 5-year survival rate. It has only been recognized in the literature since 1993.[69] This neoplasm has a fascicular, spindled "leiomyomatous" growth pattern that can show a marked degree of rhabdomyoblastic differentiation. Some tumors show marked collagen deposition. This variant occurs rarely outside the paratesticular region. These tumors are immunopositive for titin, a marker for terminal differentiation.[70]

Alveolar RMS

aRMS demonstrates a histologically distinct alveolar architecture with aggregates of small round undifferentiated cells separated by dense hyalinized fibrous septa. Crossstriations are uncommon. A review comparing IRSG pathologic diagnosis with institutional diagnosis performed between 1984 and 1997 showed concordance in only 63% of cases. The high level of discordant diagnosis (37%) reflects the need for better recognition of the solid alveolar variant of this RMS subtype. The classic cleft-like spaces lined by rhabdomyoblasts (Figure 61.3) that are traditionally described[10,12] for aRMS may merge with spaces filled with tumor cells that sit on thin fibrovascular septae. This latter solid variant is rarely present without the classic finding of cleft-like spaces and can be recognized with adequate tumor sampling. The key criterion is to recognize palisading tumor cells about fibrovascular cores. The tumor cells have a coarse chromatin pattern to their nuclei with less evident myogenesis than in eRMS.[10] FNA biopsies of aRMS demonstrate predominantly two architectural patterns, either completely dissociated cells or many chance formations of cells. However, this is nonspecific, and any RMS diagnosis on FNA requires immunohistochemical confirmation.[66]

The prognosis for both the classic and solid variants is poor, with only a 53% 5-year survival rate. Improved concordance of review and institutional diagnosis is crucial for this malignancy, as these patients receive intensified therapy on current protocols. On the analysis of 65 aRMS cases, Parham et al. concluded that there is limited correlation between the histologic assessment of aRMS and the PAX-FKHR fusion status.[71]

Anaplastic RMS

Anaplastic RMS also has a high rate (62%) of discordance.[12] Using the IRS I–III material, anaplastic RMS was defined by large, lobate hyperchromatic nuclei of at least three times the size of neighboring nuclei, and atypical multipolar mitotic figures.[12,72] It is also characterized further by its distribution as focal (group I), consisting of single or few anaplastic cells, or diffuse (group II), where anaplastic cells aggregate in clusters or form a continuous sheet.[12,72] The occurrence of anaplasia is independent of both RMS tumor site and histopathologic subtype, although it occurs

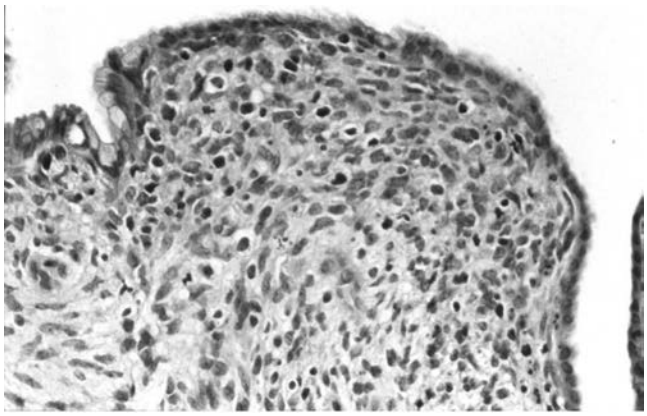

FIGURE 61.2 Botryoid embryonal rhabdomyosarcoma demonstrating the cambium (condensed layer of rhabdomyoblasts) tumor layer underlying an intact epithelium.

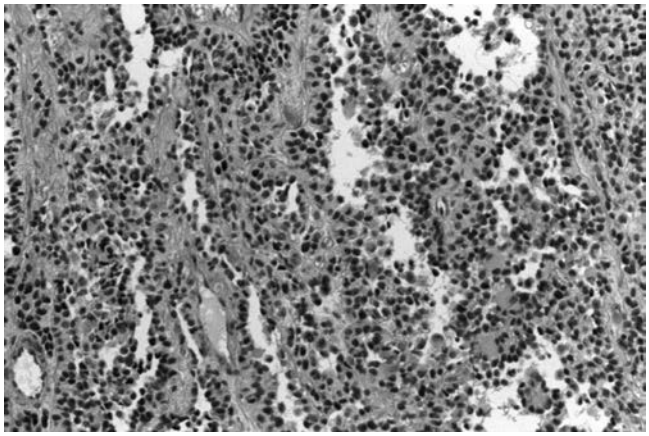

FIGURE 61.3 Alveolar rhabdomyosarcoma showing palisading of tumor cells with a coarse chromatin pattern about fibrovascular cores.

preferentially in eRMS. A recent COG analysis identified 13% of RMS cases with anaplasia, the presence of which, whether focal or diffuse, negatively influenced both OS and failure-free survival (FFS) in eRMS.[73]

Undifferentiated Sarcoma

Demonstrating a similarly high rate of discordance (62%),[12] undifferentiated sarcoma is included in the ICR system only because its response to therapy is similar to that of RMS.[10] These tumors are composed mainly of sheets of medium-packed cells with no discernible architectural structure except for delicate fibrovascular septae or a vague spindled-storiform pattern. Necrosis and inflammation are not prominent, cellularity is high with high mitotic activity (>10 mitoses per 10 hpf), and the nuclei are predominantly oval with prominent chromocenters and indistinct cytoplasm.[12,74] The tumors stain only with vimentin antisera (77%), if at all.

This entity is rare (3% of cases) and, similar to aRMS, occurs more often in males (62%) and in patients 5 years of age or older (65%), and is more common in the extremities (53%).[74] Survival with localized disease is 72%, but with disseminated disease is only 44%.[12] Early identification of this histologic subtype, enabling prompt, intensified therapy, is an important component of the IRS V studies.

Ectomesenchymoma

A rare malignant neoplasm, consisting of RMS with a neural component, ectomesenchymoma (EM) is likely underdiagnosed and has an outcome similar to that of the RMS component of the tumors. Boue et al., in their report of 15 cases, noted that there were previously only 21 other cases reported in the literature. They noted that of their 15 cases, only 2 had an originating institutional diagnosis of EM, with 12 diagnosed as RMS and 1 diagnosed as undifferentiated sarcoma. Five of these cases were of external genital origin, and six were pelvic and abdominal.[75]

Immunostaining

Ancillary histopathological tissue studies are useful for both diagnosis and prognosis. A comprehensive study using commercially available and experimental antibodies was undertaken as part of IRS IV, which included 100 cases of RMS representing all subtypes. Around 20% of RMS cases required the use of immunohistochemistry to establish the final diagnosis. Polyclonal antidesmin (P-DES) antibody was positive in all but one RMS (99%). Monoclonal antidesmin (M-DES) antibody was negative in many of the same tumors (38%). Anti-muscle-specific actin (MSA) antibody was positive in 94% of RMS. Anti-myoglobin antibody was positive in 78% and was negative mostly in the less differentiated tumors. Anti-α-smooth muscle actin (SMA) antibody reacted positively only in a minority (4%) of eRMS. The incidence of immunopositivity for the various antisera is summarized in Table 61.1.[12]

Myogenin is specific for rhabdomyoblastic differentiation and may help in the differentiation of small round cell tumors. It is strongly expressed in aRMS nuclei but demonstrates a variable staining pattern and intensity in eRMS. The extent of myogenin staining in RMS is much greater than in non-RMS tumors, making it a useful marker.[76–79] In contrast to other studies, Cessna et al. did note some rare non-RMS (7/107) focal nuclear reactivity to myogenin.[76] Pseudosarcomatous myofibroblastic tumors (PMTs) of the urogenital tract are rare benign tumors that may be mistaken for RMS. Myogenin is expressed in RMS but not PMT, and may be useful in differentiating these distinct clinical entities.[80]

MyoD1 expression is a distinguishing characteristic of RMS and reverse transcription polymerase chain reaction (RT-PCR) because *MyoD1* is highly sensitive and specific in detecting minimal residual disease, as well as bone marrow and peripheral blood stem cell involvement, regardless of histological subtype.[81]

The current approach at the IRSG Pathology Center in cases where the diagnosis of RMS is in question is to screen the case with immunostaining for three antibodies: P-DES, MSA, and MIC-2. The latter helps to rule out the diagnosis of an extraosseous Ewing's sarcoma primitive neuroectodermal tumor.[82] Around 14% of RMS stain positive to MIC-2 antisera, but this is only a weak granular intracytoplasmic immunopositivity, while Ewing's sarcoma and primitive neuroectodermal tumors show discreet plasma membrane staining.[82] Antibodies to the various myogenic transcription factors (MyoD1, etc.) are not tested because of their noted negativity with paraffin sections.[83]

While recent analysis of RMS tumor samples demonstrated only a 1.3% incidence of TP53 mutation,[84] immunopositivity at the grade 3 or 4 level (6% of RMS) was significantly associated with the occurrence of any anaplasia in aRMS and diffuse anaplasia in eRMS, independent of fusion gene status.[85]

TABLE 61.1 Incidence of immunopositivity for antisera in rhabdomyosarcoma diagnostic studies

Antibody	Percentage
Polyclonal desmin	99
Monoclonal desmin	62
Muscle-specific actin	94
α-Smooth muscle actin	4
Myoglobin	78
Wide-spectrum keratin	7
Epithelial membrane antigen	2
S-100 protein	19
Neuron-specific enolase	6
Leukocyte common antigen	0
MIC-2	14
p53	16

Posttreatment Pathologic Studies

The most difficult assessment by pathologists is the prognostic significance of residual rhabdomyoblasts in post-therapeutic RMS tissue specimens. Studies support the

concept that posttherapeutic cytodifferentiation occurs more frequently in bRMS or eRMS.[86–88] In bRMS, cytodifferentiation and decreased proliferation activity were associated with favorable outcome. Unchanged or increased posttherapeutic proliferation activity suggested aggressive biologic potential in eRMS or aRMS.

Smith et al. reported on the posttreatment cytodifferentiation and clinical outcome from 19/31 IRS IV cases that were adequate for evaluation. None of the 10 cases with extensive cytodifferentiation (2 bRMS and 8 eRMS) failed, while among the 5 cases with moderate cytodifferentiation, only the 2 aRMS patients failed, and all 4 patients (1 eRMS and 3 aRMS) with mild or no cytodifferentiation failed. The authors concluded that posttreatment cytodifferentiation is more common in both eRMS and bRMS than in aRMS, and postulated that this difference is due to different mechanisms to cellular response to therapy. They also noted that sparse persistent tumor cells in aRMS and bRMS did not appear to affect outcome.[88]

Myoglobin is specific for terminally differentiated myocytes and, as such, is a useful marker for differentiated tissue in organs such as bladder and prostate (BP), which normally do not contain skeletal muscle. As the expression of myogenin and MyoD is downregulated with terminal differentiation, they are less helpful to identify differentiated cells.[68] Sequential evaluation of six patients with pelvic (four bladder or prostate and two vulvovaginal) RMS who had persistent well-differentiated rhabdomyoblasts without mitotic activity during and after the completion of therapy demonstrated rhabdomyoblast persistence, but a decrease in number with time. All six patients were alive with no evidence of disease from 37 to 233 months after the completion of therapy. The authors conclude that while the biologic nature of these cells is not known, their presence is not an indication for further therapy.[89] Arndt et al. reached a similar conclusion upon reviewing the significance of persistent mature rhabdomyoblasts in 44 bladder or prostate RMS patients treated on IRS IV, identifying that these cells are not predictive of recurrence and their presence does not justify radical surgery.[90]

PRESENTATION

While varying with site and extent of disease, as well as the age of the patient, RMS may present as an asymptomatic mass found by patient or parents[2] and has no classic paraneoplastic syndromes.[6] Symptoms of GU RMS may include urinary tract obstruction or infection, hematuria, urinary frequency, urgency or incontinence, an abdominal mass, or constipation. Tumors of the BP typically are greater than 5 cm and invasive on presentation. Paratesticular RMS presents frequently as a scrotal or inguinal mass or swelling that might initially be diagnosed as a hernia, hydrocele, or varicocele.[6] Female genital RMS tends to be vaginal in very young girls, presenting as a mass or vaginal bleeding, while advanced uterine tumors tend to present in older girls.[6] Patients may also present with signs or symptoms of metastases (15%) or systemic signs of malignancy.[6]

A rare neonatal RMS presentation has been described with several cases reported in the literature. Frequently of alveolar subtype, it presents in neonates associated with multiple cutaneous metastases, lacking characteristic RMS translocations, and has been fatal with current therapy.[25,91] Generally, cutaneous metastasis of nonhematopoietic neoplasms is rare; however, on review, RMS was noted to be the most common pediatric neoplasm to metastasize to the skin.[92]

DIAGNOSTIC EVALUATION

In addition to a complete history and physical examination, evaluation of patients with suspected RMS should include complete blood count (CBC), urinalysis, electrolytes, calcium, phosphorous, alkaline phosphatase, lactate dehydrogenase, bilirubin A bone marrow biopsy or aspirate, and cross-sectional imaging.[6]

Imaging

The first diagnostic imaging in patients presenting with an abdominal or pelvic mass and/or symptoms of urinary obstruction is a pelvic and renal sonogram. In RMS, this will usually demonstrate a solid hyper- or hypoechoic tumor and will evaluate the status of the bladder, postvoid residual, and the upper tracts. Bladder bRMS may appear as a polypoid intraluminal mass resembling a cluster of grapes that is characteristic but not pathognomonic of this entity.[93]

The remainder of the radiographic evaluation determines the extent of the local and regional disease and identifies metastatic foci. MRI is replacing computed tomography (CT) as the examination of choice for accurate presurgical assessment of the extent and volume of disease. An accurate pretreatment tumor volume is necessary to plan for adequate radiation treatment if indicated. Extent of the tumor around the BP can be determined by MRI T2-weighted images with sagittal views demonstrating urethral tumor extent (Figures 61.4 through 61.7).[94] RMS has intermediate signal intensity on T1-weighted images and intermediate to high signal intensity on T2-weighted

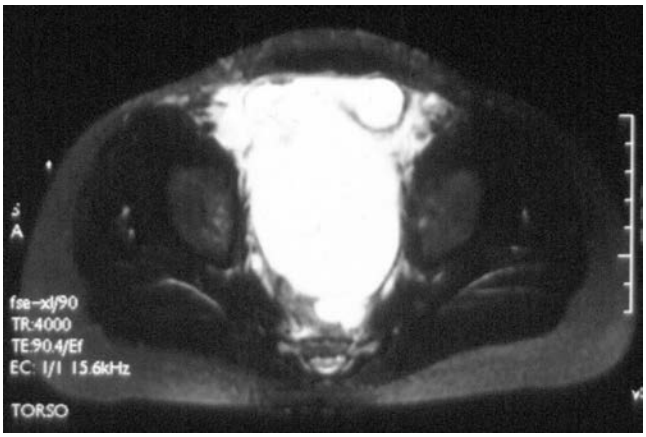

FIGURE 61.4 Magnetic resonance imaging scan finding in a 4-year-old male with embryonal group III rhabdomyosarcoma. On T2-weighted images, the extent of the tumor is well visualized.

FIGURE 61.5 Magnetic resonance imaging scan in a 4-year-old child with embryonal group III rhabdomyosarcoma. In this sagittal view, the extent of the tumor into the membranous urethra is well delineated.

images with significant enhancement with gadolinium–diethylene triamine penta-acetic acid (Gd-DTPA). aRMS demonstrates a lobular appearance on postcontrast images. While these characteristics are nonspecific and indistinguishable from other soft tissue sarcomas, MRI is useful for staging and therapeutic response assessment in RMS.[93]

FIGURE 61.6 Magnetic resonance imaging scan in a 6-year-old child with embryonal group III rhabdomyosarcoma. This sagittal view on T2-weighted image shows the extent of the tumor distally in the membranous urethra.

FIGURE 61.7 Magnetic resonance imaging scan in a 5-year-old child with embryonal group III rhabdomyosarcoma after 16 weeks chemotherapy. The tumor is visualized extending into the bladder and its extent into the urethra is also well seen.

Metastases occur most commonly to the lungs, bone, and lymph nodes, followed by bone marrow and liver. Prostatic primaries are more likely than bladder primaries to metastasize to the lungs or bone marrow.[93] A CT scan of the chest, an MRI or CT of the abdomen and pelvis, bone marrow aspiration, cerebral spinal fluid (CSF) evaluation, and if indicated, bone scan may be completed for metastatic assessment. Imaging may identify inguinal or retroperitoneal nodes, as well as pulmonary metastases. The absence of ascites does not exclude peritoneal involvement.[95]

Bone metastases in RMS are identified on imaging as ill-defined lytic lesions.[93] In a retrospective review of 301 consecutive patients from the UK Children's Cancer Study Group, only one asymptomatic patient had evidence of metastasis on bone scan in the absence of other identifiable metastatic disease. Based on these findings, McHugh and Pritchard suggest that routine bone scan may not be justified in patients without symptoms attributable to bone metastases (back or limb pain, limp, or hypercalcemia) or other demonstrable metastatic disease, but may be reserved for older patients or those with high-risk RMS, bone pain, alveolar histology, or poor prognostic sites outside of the head and neck.[96] These findings and recommendations were supported by Jager et al. in their study of 109 soft tissue sarcoma patients.[97] Bone marrow aspirate and biopsy are mandatory for IRS protocols, and bone marrow involvement at diagnosis is a poor prognosticator, with <10% survival. Any bone medullary defects noted on MRI require biopsy, even in the presence of a normal bone scan.[3] Routine CT or MRI of the head to evaluate for metastatic RMS of extracranial origin, required for IRS IV protocols, is now recommended only for clinically symptomatic patients or those with paraspinal tumors.[98]

F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT scan has been gaining attention as a potential diagnostic tool that may assist with improved

staging of RMS. Ricard et al. retrospectively reviewed the clinical utility of the addition of PET/CT to imaging protocols in the 35 staging studies for 13 children with RMS. PET/CT modified lymph node staging in four and bone involvement in two patients, resulting in treatment alteration in two patients.[99] Similarly, Tateishi et al., in a retrospective review of 35 patients, identified that FDG-PET demonstrated significantly improved overall TNM staging, as well as M staging, compared with conventional imaging alone, with a diagnostic accuracy of 89% versus 63% for M stage.[100] The CT scan is still preferred for chest evaluation, as PET is not able to reliably detect lesions less than 1 cm.[101]

Biopsy

Tissue diagnosis of RMS is confirmed by biopsy. Specimens can be obtained either endoscopically or through a needle biopsy. For endoscopic biopsy, it is preferable to utilize cold-cup biopsy forceps or a cold knife to avoid coagulation-induced histological artifacts. Alternatively, a wedge may be cut endoscopically with scissors and retrieved with grasping forceps.[102] An ultrasound-guided needle biopsy through the perineum or the extraperitoneal suprapubic route may also be used. Vaginal tumors are diagnosed and biopsied endoscopically, and the extent of distortion and/or infiltration of the bladder by the tumor can be assessed cystoscopically. Uterine tumors can be biopsied through vaginoscopy or a cervical dilatation and curettage. Open biopsy may be indicated if endoscopic or needle biopsies are inconclusive. If a laparotomy is performed, sampling of the pelvic and retroperitoneal nodes should be completed at that time.[102] Ample tissue is obtained in order to identify the histological subgroups of RMS and allow accurate grading to direct therapy. There is no requirement to excise needle biopsy sites.[6]

Brahmi et al. effectively differentiated RMS from other malignant round blue cell tumors, including Ewing's sarcoma, neuroblastoma, non-Hodgkin's lymphoma, peripheral neuroectodermal tumor, and Wilms' tumor, but not from retinoblastoma on FNA utilizing nuclear image morphometry.[103]

Urinary Diversion

Preservation of renal function requires prompt treatment of urinary obstruction. Suprapubic catheter drainage should not be used in children with RMS who present in urinary retention, to avoid the risk of tumor spread along the suprapubic tract. Usually, a urethral catheter can be utilized until chemotherapy reduces the tumor burden and the child is able to void. If possible, internalized ureteral stenting is preferable to percutaneous nephrostomy drainage to manage ureteral obstruction.

STAGING OF RHABDOMYOSARCOMA

Both the surgically based clinical grouping system (CGS) employed by the IRSG and the site-based TNM staging system have been used.[104–106] The CGS (Table 61.2) is a surgicopathologic staging system based on extent of surgical resection, with modifiers related to clinical and pathological findings.[104,105] The TNM staging system (Table 61.3) takes into account tumor location, size, clinical lymph node involvement, and the presence or absence of metastases. It is used to plan therapy and is highly predictive of outcome.[104–106]

Evaluation of tumor resection margins and the distance of the tumor from the nearest resection margins are mandatory for adequate staging. Additionally, as it affects staging and outcome, three-dimensional tumor size must be recorded at presentation. The pathologist has an important role in the staging or grouping of RMS, as well as its histopathological classification to determine appropriate risk stratification. Current COG treatment protocols are based on risk-stratified staging, and the parameters for this categorization into low-, intermediate-, or high-risk

TABLE 61.2 Clinical grouping system for rhabdomyosarcoma

Clinical group	Extent of disease	
I	**Localized, completely resected**	
	A	Confined to site of origin
	B	Infiltration beyond site of origin; no regional nodal involvement
II	**Microscopic residual or regional spread, total gross resection**	
	A	Localized with microscopic positive margins, grossly resected
	B	Regional disease with complete resection, nodal involvement, or tumor extension into adjacent organ, most distal node negative
	C	Regional disease resected with microscopic residual or most distal resected nodes involved
III	**Gross residual**	
	A	Biopsy only
	B	Gross/major primary resection (>50%)
IV	**Distant metastasis at diagnosis**	Lung, liver, bone marrow, bone, brain, distant muscle, or positive cytology CSF, pleural fluid, peritoneal fluid

TABLE 61.3 TNM staging of childhood genitourinary rhabdomyosarcoma

Stage	Sites	Tumor invasiveness	Tumor size	Regional nodes	Metastases
1	Favorable site (Paratesticular vulva, vagina, uterus)	T1 or T2	a or b	N0, N1, or NX	M0
2	Unfavorable site (Bladder, prostate retroperitoneum)	T1 or T2	a	N0 or NX	M0
3	Unfavorable site (Bladder, prostate retroperitoneum)	T1 or T2 T1 or T2	a b	N1 N0, N1, or NX	M0 M0
4	All	T1 or T2	a or b	N0 or N1	M1

Note: Tumor: T1, confined to anatomic site of origin; T2, extension and/or fixative to surrounding tissue. Size: a, <5 cm in diameter; b, >5 cm in diameter. Regional nodes: N0, not clinically involved; N1, clinically involved; NX, clinical status unknown. Metastases: M0, no distant metastasis; M1, distant metastasis present.

groups include pretreatment stage, clinical group, site, and histology (Table 61.4).[11]

TREATMENT

Local Therapy: Results of Multi-Institutional Trials

Although RMS is a chemosensitive tumor, drugs alone cannot cure most children who have this disease. Surgical resection alone or in combination with irradiation is necessary for local control of the tumor, which is essential, as nearly half of those children who die of this tumor fail locally at the primary site.

Resection

The goal of surgical resection in RMS is complete excision of the primary tumor with a surrounding rim of normal tissue, in conjunction with preservation of function. To that end, if complete resection cannot be expected without significant functional detriment, initial surgical management should be biopsy alone, with a planned second-look procedure after protocol-driven chemotherapy and/or radiation. Margins should be oriented and marked on the operative field, and areas of concern for close margins should be biopsied to verify resection completeness. Suspected residual tumor should be marked with titanium clips. Lymph node sampling is indicated for clinical or radiographically positive nodes without the need for complete lymph node resection. In cases of residual tumor, poor therapy response, or incomplete initial resection, a repeat surgical procedure after chemotherapy and radiation may be indicated.[11]

TABLE 61.4 Risk-based stratification of rhabdomyosarcoma

Risk group	Pretreatment stage	Clinical group	Site	Histology
Low 1	1 or 2 1	I or II III	Any Orbit	eRMS eRMS
Low 2	1 3	III I or II	Favorable Unfavorable	eRMS eRMS
Intermediate	2 or 3 1–3	III I–III	Unfavorable Any	eRMS aRMS
High	4	IV	Any	Any

Source: Adapted from Dasgupta R, Rodeberg DA. *Semin Pediatr Surg* 2012;21(1):68–78.

Note: Favorable sites are the GU, biliary, nonparameningeal head and neck, orbit.

GU: Bladder and Prostate

Bladder salvage may be anticipated in 50%–60%[102] of patients, and radical surgery should be delayed as long as there is continued partial response to therapy. If it is possible to preserve bladder function, such as in the case of a dome lesion, a complete resection may be performed at initial presentation through partial cystectomy with augmentation or ureteral reimplantation, if necessary. If tumor response to chemotherapy or radiation is poor, then radical cystectomy or cystoprostatectomy with continent urinary diversion may be required. On rare occasion, incomplete response of prostatic tumors to therapy may allow prostatectomy with complete gross and microscopic tumor removal and preservation of bladder function and continence. As up to 20% of cases will demonstrate positive lymph nodes, iliac and para-aortic nodes should be sampled during resection.[11]

Vulva, Vagina, and Uterus

Female genital tumors are generally responsive to primary chemotherapy, generally precluding the need for exenteration at any point in the treatment course. Nonresponsive distal vaginal lesions may not require hysterectomy; however, hysterectomy should be considered for proximal vaginal tumors, and those of the uterus as primary uterine tumors may be less chemosensitive. Ovaries should be preserved unless there is direct tumor involvement.[11] Vaginal tumors rarely spread to regional lymph nodes; however, uterine tumors are frequently quite extensive at diagnosis.[6]

Retroperitoneum and Pelvis

Typically large at presentation, and carrying a poor prognosis, retroperitoneal and pelvic tumors may be primarily resected if a safe resection is expected with preservation of function. A review of patients with clinical group III or IV RMS of the non-GU pelvis or retroperitoneum enrolled in IRS III or IV pilot identified that patients with eRMS who underwent a debulking procedure had improved 4-year FFS rates compared with the biopsy-alone group (72% vs. 48%).[107] In patients with localized RMS of the pelvis or retroperitoneum outside the GU tract in IRS IV, there was improved survival in those patients who underwent primary resection or debulking of at least 50% of the tumor burden compared with those with initial biopsy only and second-look operation following chemotherapy and radiation. Some concern has been raised that this particular group of patients had poor compliance with RT protocol, and this may have contributed to decreased local control for the biopsy group.[108] Therefore, cautious consideration may be given to a debulking procedure for tumors in these sites.

Perineum and Perianal

Often large at presentation, perineal and perianal tumors should undergo complete resection if function can be preserved, particularly continence. A temporary colostomy may be needed to manage anorectal obstruction.[11]

Paratesticular

Paratesticular RMS should be managed with radical inguinal orchiectomy, employing proximal spermatic cord control prior to cord and testicular manipulation. If indicated, biopsy should be obtained only after proximal cord control, with isolation of mobilized testicle and cord from the wound with nonpermeable drapes, and tumor spillage (to include hydrocele fluid) should be avoided. In any case where unprotected tumor spillage occurs, patients are classified as at least clinical group IIA.[109] Hemiscrotectomy should be completed at the time of orchiectomy for any patient who had a history of a transscrotal biopsy. All patients should undergo thin-cut staging CT of the abdomen and pelvis to assess for retroperitoneal node involvement. Patients less than 10 years of age with no clinical evidence of nodal involvement do not require retroperitoneal lymph node dissection (RPLND); however, those greater than 10 years or with evidence of retroperitoneal nodal disease on CT scan should undergo staging ipsilateral nerve-sparing RPLND to include sampling of suprarenal nodes, as positive suprarenal nodes result in upstaging to clinical group IV.[11] Tomaszewski et al. reported on a case series of three patients in whom laparoscopic RPLND was completed with the benefits of a rapid convalescence and minimal delay before commencing adjuvant chemotherapy.[110]

Chemotherapy

Primary chemotherapeutic agents in the treatment of RMS include vincristine, dactinomycin, and cyclophosphamide (VAC). Modifications of the standard VAC regimen based on risk stratification are ongoing through the COG to identify regimens with decreased treatment burden and preserved survival for patients with low-risk disease, and options for novel therapies and dose intensification to improve response and survival in patients with high-risk disease.

Additional Chemotherapeutic Agents

Doxorubicin

IRS I, II, and III randomized group III and IV tumor patients to VAC with or without doxorubicin with similar radiation therapy (XRT) with no benefit to doxorubicin detected.

Cisplatin and Etoposide

IRS III evaluated VAC versus VAC, doxorubicin plus cisplatin versus VAC, doxorubicin, and cisplatin plus etoposide, with all patients receiving XRT with no benefit of any of the additional agents over VAC alone.

Ifosfamide

Severe acute renal tubular toxicity was noted for ifosfamide when combined with carboplatin in children with sarcomas compared with ifosfamide alone or with cisplatin, while combination use with cisplatin was associated with delayed renal tubular toxicity.[111] Skinner et al. identified risk factors associated with nephrotoxicity from ifosfamide in 148 young sarcoma patients. Reduction of risk for nephrotoxicity was noted with doses less than 84 g/m^2, while doses greater than 119 g/m^2 were associated with a very high risk of severe toxicity.[112] Ifosfamide did not improve outcome for patients with nonmetastatic disease when substituted for cyclophosphamide in IRS IV.[113]

Melphalan

Melphalan is active in previously untreated RMS and was combined with vincristine in IRS IV in comparison with ifosfamide and etoposide (IE), and ifosfamide and DOX for metastatic disease in an up-front window. Despite high response rates, the melphalan group required more dose reduction of cyclophosphamide and had higher rates of secondary malignancy, with inferior OS.[114,115]

Topotecan

Chastagner et al. reported that topotecan potentiates the radiation response of two different human RMS tumors xenografted into nude mice.[116] Topotecan administered to 40 patients with stage 4 RMS resulted in 45% complete and partial response rates.[114] Fifteen patients with recurrent or refractory RMS were treated with a combination of topotecan and cyclophosphamide, with 10 achieving a partial or complete response.[117] Despite the apparent efficacy in metastatic and recurrent RMS, COG study D9803 did not identify a treatment advantage with the addition of topotecan to the treatment regimen for intermediate-risk RMS, with no improvement in FFS when alternating standard VAC with vincristine, topotecan, and cyclophosphamide (VTC).[118]

Irinotecan

RMS xenografts from untreated patients, as well as those that were resistant to vincristine, melphalan, and topotecan, have responded to irinotecan, a camptothecin analog.[119]

COOPERATIVE TRIALS

The outcome of children with RMS has improved dramatically over the past 40 years. In the 1960s, when therapy was local in the form of surgery and irradiation, only around one-third of all patients survived.[120] The subgroup of patients with tumors in selected primary sites, such as the bladder or the orbit, was treated with radical surgery with 70% survival.[121–123] During the 1960s, combined chemotherapy was initiated with VAC, yielding promising results.[124,125] These early encouraging results, combined with the heterogeneity and rarity of RMS, prompted implementation in 1972 of the first national cooperative trial.

IRS I–IV

The IRS committee has reported the results of four consecutive trials encompassing 3630 patients: IRS I (1972–1978, $n = 686$), IRS II (1978–1984, $n = 999$), IRS III (1984–1991, $n = 1062$), and IRS IV (1991–1997, $n = 883$).[9,113,126,127] The estimated 5-year OS rates steadily and significantly increased in each of the first three trials: 55% in IRS I, 63% in IRS II, and 71% in IRS III, while the fourth trial only showed benefit over prior studies in specific subgroups of intermediate-risk eRMS with a 3-year OS of 86%.[113] Highlighting the need for long-term follow-up of these cohorts, a recent long-term analysis of the Italian Cooperative Study RMS 79 (1979 through 1987), which initially identified a 63% 3-year OS, identified a decrease in OS to 53% at 20 years, with a median follow-up of 23 years. Characteristics influencing long-term survival were histology, tumor site and size, and IRS group.[128]

In IRS I treatment, assignment was based on the post-surgical extent of disease, with no stratification for specific risk subgroups. IRS II study recognized the prognostic significance of certain risk factors (clinical group, site, and histology) and stratified patients accordingly. Patients with primary tumors in "special pelvic" sites (bladder, prostate, vagina, and uterus) received VAC chemotherapy. IRS III further stratified patients into nine distinct risk subgroups according to extent of disease, primary tumor site, and histology. IRS IV evaluated new up-front window chemotherapy regimens and the effectiveness of hyperfractionated RT compared with conventional radiation.[113,129–131]

Clinical Group I

Given the overall expected excellent prognosis of clinical group I (completely resected) RMS, studies evaluated progressive options to decrease therapy burden. In IRS I, it was concluded that the 5-year OS and disease-free survival did not change with the addition of RT to VAC chemotherapy, resulting in the omission of RT for children with clinical group I tumors.[126] IRS II demonstrated equivalency between vincristine and dactinomycin (VA) chemotherapy and VAC chemotherapy for clinical group I patients. In IRS III, the 5-year progression-free survival (PFS) and OS for those treated with VA for 1 year were similar to those for VAC or VA for 2 years.[9] With an increased cyclophosphamide and ifosfamide intensity over IRS III, IRS IV demonstrated improved 3- year FFS in group I and II unfavorable-site eRMS from 71% to 86%.[132] These combined results produced treatment recommendations that patients with completely resected eRMS at favorable sites (GU nonbladder prostate) be treated safely and effectively with two drugs (VA) for 1 year. Those with bladder or prostate group I eRMS receive VAC, potentially at an intensified cyclophosphamide dose, and those with aRMS or undifferentiated RMS receive XRT in addition to VAC.[132]

Clinical Group II

Clnical group II RMS patients usually received postoperative RT at various time points during treatment, resulting in a local control rate of 90%.[9,126,127] Based on IRS I and II study results, VA with RT remained the therapeutic standard for children with clinical group II disease presenting with a favorable-histology tumor in a favorable site. IRS III compared VA plus adriamycin and RT with VA only plus RT. Even though there seemed to be an advantage to adding adriamycin, this was not statistically significant.[9] The CWS reviewed the benefits of RT for group II patients over four trials from 1981 to 1998. In this study of 203 group II patients, 110 received XRT and 93 did not. Local control rates were 83% with and 65% without RT ($p < 0.004$), while the OS difference was not statistically significant (84% vs. 77%). In these studies, the distribution of patients with unfavorable histology or sites was significantly higher in the groups that received RT than in those that did not, and despite this difference, the trends were for better outcome in the groups that received RT. This group was not able to identify a subset of group II patients in whom RT may be spared.[133]

IRS IV evaluated higher-dose cyclophosphamide, as well as IE, resulting in similar survivals for patients with local or regional tumors in all IRS IV treatment groups, with a lower overall toxic death rate in IRS IV (1%). However, IRS IV was associated with more improved OS and FFS than IRS III for the subgroup of patients with intermediate-risk (stage 2 or 3/group I or II) eRMS (93% vs. 76% 3-year FFS).[113]

As part of the Italian Cooperative Study RMS 88, 25 patients with microscopic residual RMS after primary excision were reviewed. Microscopic residuals were difficult to manage because of the lack of a measurable target. Primary reexcision with chemotherapy was the treatment of choice for children less than 3 years who could not receive radiation. It was not effective for tumors larger than 5 cm, where adequate RT and chemotherapy were found to be effective.[134]

Unfavorable-Histology Clinical Group I and II Tumors

The poor outcome for children with clinical group I aRMS was recognized in IRS I.[126] Therefore, these children received intensive VAC chemotherapy in IRS II, resulting in increasing the 3-year disease-free survival rate from 43% to 69%.[127] In IRS III, therapy was further intensified with the use of a regimen containing VAC with doxorubicin (VADRC), VAC, and cisplatin. The 5-year PFS ($71 \pm 6\%$) and OS (80 ± 6) rates were significantly improved over those for comparable patients treated on IRS II protocols.[9]

Despite an intensified chemotherapy regimen in IRS III compared with the first two studies, patients with unfavorable histology (alveolar or undifferentiated) who did

not receive radiation fared worse than those who received radiation in this study or historically. Pooled data from IRS I, II, and III on all undifferentiated RMS and aRMS demonstrated that radiation was associated with improved FFS (73% vs. 44%, 10 years, $p = 0.03$) with fewer local, regional, and distant relapses.[45] In review of IRS I, II, and III group I patients, Wolden et al. identified that tumors of >5 cm and alveolar histology were associated with poorer FFS. The GU primary site conferred both an OS and an FFS advantage for eRMS, but not for aRMS or undifferentiated sarcoma.[135] IRS IV found no improved survival in aRMS compared with IRS III.[113] Localized aRMS at any site is currently classified as at least an intermediate-risk tumor for COG protocols (Table 61.4).

Clinical Group III

This is the largest group of patients enrolled in IRS I, II, and III.[126,127,136] In IRS I, all group III patients were randomized to receive either VAC and radiation, or VADRC-VAC and radiation. Addition of doxorubicin failed to improve the 5-year OS.[126] IRS II patients were randomized to receive intensified VAC or VADRC-VA therapy. Prognosis was not different between those two regimens, but the intensified treatments were superior in inducing complete responses and prolonged survival compared with IRS I.[127] IRS III patients were randomized to receive either pulsed VAC or VADRC-VAC-cisplatin or VADRC-VAC-cisplatin-VP-16. At 5 years, the OS was the same for all three regimens.[9] Several patients among these study arms received alternate induction chemotherapy with one of three drug pairs (doxorubicin-dacarbazine, dactinomycin-VP-16, or dactinomycin-dacarbazine) and second-look surgery.[9,136] The outcome of these children was improved compared with that of patients who were treated in IRS II. IRS IV regimens including IE and higher cyclophosphamide doses than in IRS III resulted in similar outcomes for group III patients among the IRS IV treatment groups and between IRS III and IRS IV. The standard remains VAC and RT for these patients.[113] While unfavorable-site group III patients demonstrated no improvement in survival on IRS IV compared with IRS III, the subset of group III or resectable node-positive eRMS with a GU nonbladder or prostate primary improved from a 72% to 92% 3-year FFS.[132]

Clinical Group IV

With the exception of a subset of intermediate-risk patients (<10 years old, embryonal), the 5-year survival for patients with metastatic disease continues to be poor, in spite of intensified therapy and new drug combinations. The combined agent regimens in the first three IRS studies led to 5-year OS and PFS rates below 30%.[9,126,127]

In a pilot study for IRS IV, doxorubicin and ifosfamide were used in an up-front window prior to VAC for metastatic RMS, resulting in an ultimate complete response rate of 53% and 1/3 survival, similar to prior regimens. Factors in this study contributing to a better prognosis included age less than 10, embryonal histology, GU primary, lack of nodal disease, and absence of bone or bone marrow metastasis.[137] IRS IV evaluated the effectiveness of an up-front window of IE compared with vincristine and melphalan (VM) for metastatic presentations. This initial therapy was followed by VAC, surgery, and RT, and then a repeat of VM or IE in initial responders. While initial response in both groups was high, OS was better in the IE group, with a 3-year FFS and OS of 33% and 55%, compared with 19% and 27% for the VM group.[115] A retrospective multivariate analysis of 137 group IV patients enrolled in IRS IV identified the presence of two or fewer metastatic sites as a predictor of survival. The subgroup with embryonal histology and two or fewer metastatic sites demonstrated a 3-year FFS of 40% and OS of 47%, compared with 25% and 39% for all patients studied. The authors suggest that this subgroup, whose survival approaches that of selected patients with nonmetastatic disease, might not be appropriate candidates for consideration in highly toxic or unproven antitumor investigational regimens.[130]

Treatment of 48 patients with metastatic RMS with topotecan in an up-front window prior to VAC and continued for responders resulted in a 46% overall response rate with an acceptable toxicity profile. Particularly interesting was that efficacy was greater against aRMS than eRMS (65% vs. 28% response, $p = 0.08$).[138]

The European Collaborative Studies MMT 4-89 and MMT 4-91 failed to demonstrate a statistically significant improvement in the 3-year EFS comparing consolidative megatherapy (high-dose chemotherapy and stem cell rescue) and standard chemotherapy (30% vs. 19% of 53 and 44 patients) in the treatment of metastatic disease.[139] The lack of benefit of this modality was verified by Weigel et al., who completed a meta-analysis of 389 metastatic RMS patients treated with high-dose chemotherapy and stem cell rescue, and confirmed that this treatment conferred no survival advantage for stage 4 patients compared with IRS II and III.[140] Further evaluation of intensive chemotherapy in MMT 98[141] and RMS 4.99[142] conferred no additional benefit for poor-risk patients.

Regional Lymph Node Disease

Histologically proven lymphatic involvement in the presence of localized RMS with a grossly complete resection in IRS I and II was most common in prostate (41%) and paratesticular (26%) RMS, with an overall rate of 24% for GU sites.[143] IRS III identified nodal disease as an independent prognosticator only in stage 3 aRMS.[144] Rodeberg et al. evaluated the prognostic significance of regional lymph node disease for children enrolled in IRS IV with a comparison of N0 disease, clinically or pathologically confirmed N1 disease, and single-site metastatic disease. Poorer prognosticators were identified in the patients with N1 disease who were more likely to be older than 10, and have unfavorable primary sites, alveolar histology, higher stage and clinical group, and large invasive primary tumors. FFS for N1 disease was statistically significantly different from both N0 and single-site metastatic disease, falling between the two. Substratification by tumor histology results in outcomes for N1 aRMS similar to those of metastatic disease, with both significantly worse than N0 aRMS, while eRMS patients had similar outcomes regardless of nodal status, which were significantly better than those with a single metastatic focus. Outcome predictors differed between aRMS and eRMS, with node status being the only significant predictor of

FFS and OS in aRMS, whereas eRMS demonstrated patient age, tumor invasion and primary site, and metastatic disease as predictive factors. Gene array analysis in this study also noted increased expression of immune response genes in node-positive aRMS. The authors recommend consideration for treatment intensification for node-positive aRMS and conclude that node-positive disease is not being overtreated.[145]

Radiation Therapy

RT provides another option for local control in those patients whose primary tumor is not amenable to resection, or who have residual microscopic (group II) or gross (group III) disease after resection. In response to the results of several trials, RT doses now vary according to the patient age, tumor site, and amount of residual tumor.[8] Intensified chemotherapy and second-look surgery have decreased the use of RT and extensive primary surgery for patients with vaginal and vulvar RMS.[146] In addition, the use of early RT, aggressive chemotherapy, and second-look surgery has dramatically decreased the use of radical surgery to treat children with GU RMS.[9,146]

In IRS IV, RT of completely resected tumors with unfavorable features (large size, unfavorable site, and nodal involvement) was mandated, with gross residual disease requiring higher doses of 45–55 Gy, depending on the site and size of the tumor.[8,38] Further, to increase local control and decrease the acute and late adverse effects of RT, IRS IV evaluated hyperfractionated RT in patients with unresectable or metastatic disease. A total of 559 patients were enrolled with group III RMS, of which 478 were eligible for randomization to standard (239) or HFRT (239). There was no statistical difference in OS or FFS between the two radiation treatment methods, and no difference between the two treatment groups when analyzed for age, gender, tumor size, invasiveness, nodal status, histology, or primary site.[130]

Risk-Stratified Protocols

Meza et al. reviewed outcomes from IRS III and IV to identify prognosticators in nonmetastatic disease. Overall, aRMS had a worse outcome than eRMS (5-year FFS of 65% vs. 82%). FFS in aRMS was influenced by stage, grade, age of <1 year, and locoregional lymph node involvement. Three prognostic subsets of eRMS were identified from IRS III and IV to guide risk stratification in successive studies. Nonmetastatic eRMS at favorable sites are completely resected eRMS at nonfavorable sites are low-risk tumors that were classified into two subsets. Subset A (stage 1/group I or IIA, stage 2/group I and group III orbit), with a 5-year FFS of 90%, had an excellent outcome with modest therapy on IRS III–IV. Subset B (stage 1/group IIB or IIC, stage 1/group III nonorbit) demonstrated a 5-year FFS of 87%; however, those in the subset who received two-drug therapy (VA) had poorer outcomes and were excluded from analysis. Subsequent protocols including VAC therapy resulted in a similar excellent outcome for subset B patients. The remaining patients (stage 2 or 3/group III eRMS) were classified as intermediate risk (5-year FFS of 73%).[144]

IRS V, now also named the Soft Tissue Sarcoma Committee of the COG, continued cooperative studies with the recently completed D series (D9602, D9802, and D9803) focusing on risk-adapted therapy.[147] This approach continues with the current risk-stratified protocols ARST0331 (low risk), ARST0531 (intermediate risk), and ARST0431 (high risk) (Table 61.4).

FFS is estimated to be 90% at 5 years for low-risk RMS[144] and 70% at 4 years for intermediate-risk RMS.[118] The 3-year OS is estimated to be 30% for high-risk RMS.[101,148]

Low-Risk RMS

Given their relatively excellent survival estimates, the objectives of low-risk protocols are primarily to decrease treatment burden. COG D9602 (1997–2004) was designed to decrease toxicity in localized, grossly resected eRMS by reducing RT and eliminating cyclophosphamide. The lowest-risk patients, subgroup A (stage 1/group I or IIA, stage 2/group I and group III orbit) received VA with a 5-year FFS of 95% and subgroup B (stage 1/group IIB or IIC, stage 2/group II, stage 3/group I or II) received VAC with a 5-year FFS of 85%. Group II or III patients received RT that was reduced compared with IRS IV from 41.4 to 36 Gy for the lower-risk stage 1/group IIA patients. The 5-year FFS rate of 89% for subgroup A and 85% for subgroup B were similar to those of IRS III, despite lower RT doses; however, they were decreased from those of similar patients in IRS IV who received VA plus cyclophosphamide.[149]

Breneman et al. reviewed the efficacy of RT dose reduction on local control for these patients. Low-risk patients were substratified for different RT doses. Group I received no RT, and group III underwent second-look operation. Postoperative RT was given for residual gross or microscopic tumor for group III vaginal RMS patients, and other group III patients received a second-look operation if complete resection was possible without significant functional or cosmetic deficit, followed by fractionated RT with a 1.5 cm margin. Group IIA patients received reduced-dose RT at 36 Gy. Groups IIB and IIC received 41.4 Gy, and group III without second look received 50.4 Gy. After the second-look procedure, patients received 36–50 Gy, with the exception of girls with vaginal tumors, who were spared RT if second-look operation had negative margins. RT dose reduction to 36 Gy, from 41.4 in IRS III and IV, with cyclophosphamide chemotherapy for the unfavorable-site group IIA tumor patients resulted in no local failures at 5 years compared with 14% and 7% in the two prior trials, suggesting no increase in local failure with RT dose reduction for this subgroup of patients.[147] Based on a subgroup analysis identifying 60% locoregional failure rates in girls with group IIA RMS vaginal primaries with protocol-specified omission of RT, current trials mandate RT for group II or III vaginal tumors at 36–50.4 Gy.

The current low-risk protocol COG ARST0331 redefines the low-risk subsets based on the subgroup analysis of D9602, demonstrating that within subset B, patients with stage 1/group IIB or IIC or stage 2/group II had similar OS rates with VA on IRS III and VAC on IRS IV. This subgroup has been shifted to the lowest-risk subset. The two low-risk eRMS subsets to be evaluated include

subset 1 (stage 1 or 2/group I or II) and subset 2 (stage 1/group III, stage 3/group I or II). The lowest-risk patients (subset 1) will receive VAC for four cycles with a reduced dose of cyclophosphamide, followed by VA for four cycles with radiation, resulting in a reduction of therapy length to 22 weeks. Subset 2 will be treated with an additional eight cycles of VA for a total of 12 after the VAC with reduced cyclophosphamide. Additionally, the protocol will assess lower-dose (3600 cGy) radiation for node-negative patients with microscopic residual disease and dose–response radiation dosing after second-look surgery for group III patients.

Intermediate-Risk RMS

From 1999 to 2005, COG D9803 randomized 516 intermediate-risk patients to VAC or VAC alternating with VTC. Patients received response-adjusted RT according to stage, group, and histology at diagnosis, as well as disease status at second-look surgery. The 4-year OS and FFS were unchanged from those of IRS IV on any treatment regimen. VAC was associated with a higher incidence of febrile neutopenia. The trial confirmed prior findings of higher failure rates with increased stage and group and with alveolar histology.[118] Twenty patients in this protocol (2.2%) demonstrated early disease progression and did not receive planned protocol RT (19/20 at the primary site), with a 5-year OS for this group of 32% compared with historical data for recurrent disease (OS of 20%). The authors theorize that earlier RT timing might result in better local control.[150]

Lin et al. compared the outcome of patients enrolled in COG D9803 and treated with intensity-modulated radiotherapy (IMRT) with those treated with three-dimensional conformal radiotherapy (3D-CRT) and did not identify any significant difference in locoregional control or FFS; however, they did identify that IMRT resulted in improved target dose coverage. Improved dose coverage with IMRT may enable a lower treatment dose with preserved efficacy in future trials.[151]

Dharmarajan et al. studied the toxicity and efficacy of irinotecan and carboplatin delivered concurrently with RT for intermediate- and high-risk RMS in a single-institution pilot phase II trial from 2003 to 2011, with preliminary results demonstrating local control rates of 89% at 2.5 years, comparable to D9803 despite the inclusion of high-risk in addition to intermediate-risk patients in this trial. In addition to excellent local control rates, the regimen resulted in a favorable toxicity profile.[152]

COG trial ARST0531 is currently enrolling intermediate-risk patients in a trial evaluating the response rates and FFS for those treated with VAC or VAC alternating with vincristine and irinotecan (VI), and early versus late RT.

High-Risk RMS

International Society of Pediatric Oncology (SIOP) study MMT 95 evaluated intensified chemotherapy for 457 high-risk nonmetastatic RMS and soft tissue sarcoma patients to receive ifosfamide, vincristine, and dactinomycin (IVA) or an intensified six-drug regimen of IVA plus carboplatin, epirubicin, and etoposide. The 3-year OS was similar between the two arms (82% IVA and 80% six-drug), with a significantly greater treatment toxicity in the six-drug group.[153]

In successive trials COG 9802 (19 patients) and 9802R (50 patients), irinotecan and then irinotecan in combination with vincristine were assessed for efficacy and toxicity in the treatment of metastatic RMS in an up-front window trial. After the initial treatment window, partial and complete responders continued to receive irinotecan with or without vincristine alternating with VAC, while nonresponders continued with VAC. Irinotecan alone resulted in a window response rate of 42%, but a progressive disease rate of 32% resulted in the closure of COG 9802 (irinotecan alone) and modification to 9802R (irinotecan and vincristine), with improvement in the window response to 70% and reduction in progressive disease to 8%. This response rate surpassed that of the prior window trial and demonstrated lower disease progression than VAC alone, despite no improvement in survival. The primary toxicity of the window treatment was gastrointestinal (predominantly diarrhea and abdominal pain), and there were fewer grade 3 and 4 toxicities in the window treatment group (50%) than in the VAC group (80%). The authors conclude that the lack of cross-resistance and the overlapping toxicity profiles of VI and VAC, in combination with the response rate to VI, warrant irinotecan in combination with vincristine integration into RMS treatment protocols.[154]

COG ARTS0431 is evaluating the efficacy of intensive interval compression of known RMS effective agents (including ifosfamide, etoposide, doxorubicin, and irinotecan, in addition to VAC) to improve early disease control and the feasibility and side effects of irinotecan administered in combination with radiation.

Despite improved outcomes for localized disease, the prognosis for patients presenting with metastatic disease has not improved significantly over the past 20 years, with an overall cure rate below 30%.[148] Oberlin et al. pooled data from IRS II–V, IRS D9501, Italian Group (RMS 4.99), SIOP MMT (84 and 98), and European Intergroup (MMT 89–91) to evaluate prognostic factors for 788 patients presenting with metastatic RMS and treated between 1984 and 2000.[148] Metastases were most common to the lung (47%), with this being the only metastatic site for 18%, followed by bone marrow, bone, and distant nodes. The estimated overall 3-year EFS and OS were 34% and 27%, respectively, with no significant difference between American and European groups. Multivariate analysis identified age less than 1 or greater than 10 years, unfavorable primary site, bone or bone marrow involvement, and three or more metastatic sites as independent risk factors decreasing EFS. The 3-year EFS decreased from 50% for no risk factor to 42%, 18%, 12%, and 5%, respectively, for the addition of one to four risk factors.

Special Pelvic Tumors

Early in the IRS studies, it became apparent that certain pelvic tumors (bladder, prostate, vagina, and uterus) responded better to therapy than other sites. In IRS I, treatment for BP RMS included primary exenteration, followed by a 2-year course of chemotherapy and local RT.[155,156] The 5-year OS in this group of patients was

74%. However, this outcome was achieved at the expense of numerous bladder extirpations for patients with GU tumors, and only 23% of the patients had functional bladders 3 years after therapy.[156] In IRS II, the treatment strategy changed to primary chemotherapy with 4 months of VAC, followed by delayed radiation and/or surgery. This treatment approach failed to improve the bladder salvage rate, with a 3-year bladder retention rate of only 25% and a survival rate similar to that of IRS I.[157,158] Outcomes were similar to those of SIOP and the Italian Cooperative Group (ICG), where radiation treatment was delayed until after the chemotherapy response was assessed, and only instituted if there was inadequate response to chemotherapy.[131] In IRS III, patients in clinical group III received an intensified VADRC-VAC regimen plus cisplatin to induce a complete response. Second-look surgery was recommended at 20 weeks. Alternate induction therapy with dactinomycin and VP-16 was initiated if tumor remained. The 3-year bladder preservation rate (60%), 5-year PFS estimate ($74 \pm 5\%$), and OS (83 ± 4) were strikingly superior to those of IRS I and IRS II.[9,126,127]

Bladder and Prostate

Prior to multiagent chemotherapy, BP RMS was treated with radical cystectomy or pelvic exenteration. Encouraging results with primary chemotherapy have prompted a paradigm shift toward organ preservation when possible, without negatively impacting long-term survival. While outcomes for RMS have improved across the four IRS trials, outcomes for nonmetastatic BP RMS have been relatively constant, with 78%–82% survival.[129,159] This is similar to international cohorts (SIOP, ICG, and CWS), which demonstrated an OS rate of 84%.[129,160,161] Survival rates have remained stable despite a marked decreased in the rate of cystectomy from 78% to 9%.[129,159] Improvements in chemotherapy regimens have imparted better OS rates despite less aggressive surgery resulting in higher bladder retention rates.[129,131]

Heyn reviewed the outcome of 28 patients with group III bladder RMS. All received 20 weeks of multiagent chemotherapy and 4 weeks of RT. Of these, 13 underwent cystectomy. Cystectomy specimens demonstrated diminished tumor cells with varying degrees of maturation. They concluded that primary bladder RMS is very responsive to chemotherapy and RT, and that these tumors show further maturation following treatment, thus allowing preservation of larger proportions of bladders with residual disease.[86] Similarly, Lobe et al. examined the role of conservative surgery in localized prostatic RMS and showed a high cure rate with relatively good bladder salvage rate without aggressive early surgery.[162]

Arndt et al. reported the results from IRS IV and reviewed bladder function retention with a bladder preservation approach in patients with nonmetastatic BP RMS. Of 90 patients with nonmetastatic BP RMS, 88 had sufficient information for review. Tumor characteristics included 70% arising from the bladder, 80% favorable histology (eRMS or bRMS), 69% greater than 5 cm in diameter, 84% group III, and 56% invasive T2 tumors. All patients received alkylating-based chemotherapy, and 74 received radiation. As one of the goals of the protocol was organ preservation, initial radical resection was not recommended. Patients underwent initial biopsy with initial complete resection only if organ preservation was possible. Extirpation was reserved for biopsy-proven residual disease after completion of therapy, or progression of disease and early treatment failure after chemotherapy and XRT. OS and EFS rates at a median follow-up of 6.1 years were 82% and 77%. Events included 3 second malignancies, 1 toxic death, and 18 relapses (14 [78%] deaths with relapse). The bladder preservation rate was 83%, with 55% of retained bladders maintaining normal bladder function (lack of incontinence, dribbling, hydronephrosis, or enuresis after age 10) at a median follow-up of 9 years. Of all the patients entered in the study, 40% (36 of 88) survived event-free with apparently normal-functioning bladders. The authors advocate conservative delayed surgery in this group of patients and, recognizing that radiation treatment may have late effects, state that more precise long-term evaluation of bladder and sexual function will be required, using such tools as urodynamic studies and validated patient surveys.[129]

A retrospective chart review of 309 patients with BP RMS treated on IRS IV, SIOP MMT 84 and 89, Italian Cooperative Group RMS 79 and 88, and the German Cooperative Weichteilsarkonstudie 91 and 96 protocols resulted in 164 patients with enough data to assess late sequelae. Seventy-nine percent of 145 patients retained all or part of their bladder. Forty-three (69%) out of the 62 patients who did not undergo cystectomy and were older than 6 years had no recorded continence issues, while 19 (31%) cited at least one issue with bladder function, including nighttime incontinence, daytime incontinence, frequency, and urgency. Additional urologic sequelae included recurrent urinary tract infections, renal insufficiency, chronic hematuria, hydronephrosis, vesicoureteral reflux, urolithiasis, and hydroceles. Of males old enough to assess sexual function, 25/27 were capable of attaining erections, and 16/20 were capable of ejaculation. Two patients developed secondary tumors, including a breast cancer and a schwannoma of the leg.[163]

Seitz et al. evaluated the outcomes of patients with localized BP eRMS enrolled across 42 institutions in the CWS 96 trial between 1996 and 2002. The trial enrolled 69 patients with localized BP eRMS, with six exclusions due to incomplete data. The treatment protocol included risk-adjusted chemotherapy regimen of at least three drugs. Standard risk tumors were treated with IVA, and high-risk tumors were randomized to vincristine, ifosfamide, doxorubicin, and dactinomycin (VAIA) versus carboplatin, epirubicin, vincristine, dactinomycin, ifosfamide, and etoposide (CEVAIE). The majority were IRS group III patients, and radiographic response was assessed after 9 weeks, with subsequent local treatment driven by tumor volume reduction. Hyperfractionated accelerated radiotherapy (HART) was risk stratified based on chemotherapy response or postoperative tumor status. Complete or good responders with eRMS were treated with 32 Gy, and poor responders received 44.8 Gy. HART noncandidates received conventional fractionation at 39.8 or 50 Gy. Clinical group I patients did not receive RT. Thirty-eight (60.3%) patients were irradiated with equivalent EFS and OS between the risk-stratified dosing

groups, demonstrating no decrease in response with lower doses in the lower-risk group and a 50% early complication rate from treatment. Initial tumor biopsy was completed in 51 patients with a 9.8% complication rate, and 25% of the 12 who underwent primary tumor resection had a complication. Secondary surgery was completed in 45 patients with a 28.8% complication rate, and bladder preservation was not possible in 17 of them. The 5-year OS for all patients was 76% and was equivalent across all treatment groups except for the primary incomplete resection group treated with postoperative radiochemotherapy, which was significantly lower (84%–88% vs. 40% 5-year OS). Fourteen patients suffered a local relapse (6/14 after incomplete primary or secondary resection with no RT) at a rate higher than IRS IV. Given the unfavorable outcome, risk of incomplete resection, and a complication rate 2.5 times higher than in other groups, the authors recommend biopsy as the primary surgical approach, rather than primary surgery, unless a complete resection with negative microscopic disease is feasible. Secondary local control may be completed with risk adaption protocols to limit treatment-related morbidity.[159]

Rodeberg et al. compared the outcomes for BP RMS across four international study groups comprising 379 protocol patients treated from 1979 to 1998: IRS IV, SIOP Malignant Mesenchymal Tumors Committee (SIOP MMT 84 and 89), ICG RMS 79 and 88, and German CWS 91 study. Across protocols, patients received similar chemotherapy regimens, with recommendation for avoidance of radical resections. RT differed among the studies, with IRS and CWS patients receiving risk-stratified RT for incomplete resection. SIOP treated with RT those patients without complete response radiographically, and ICG required a negative histologic second look to avoid RT. Primary tumor resection was grossly complete in 5% of all cases and attempted in only 12% (40% successful complete primary resection). Forty-eight percent of SIOP and ICG and 85% of IRS IV and CWS localized BP eRMS patients received RT as initial treatment of primary tumor. The 5-year FFS was 75%, with the OS estimated at 83%. Multivariate analysis identified a tumor size of >5 cm (RR 2.3) and tumor invasion (RR 1.6) as independently predictive of FFS, and a tumor size of >5 cm as predictive of OS. The 5-year FFS differences among protocols (ICG 81%, IRS 79%, SIOP 65%, and CWS 70%) were not statistically significant, and the 5-year OS was similar among all groups (79%–83%). As expected, nonembryonal localized BP RMS and metastatic BP RMS resulted in poorer outcomes (5-year FFS and OS both 47% for non-eRMS and 41% and 44% for metastatic). Similar to other sites, metastatic BP RMS was associated with larger invasive tumors, and positive nodes in children less than 1 year or greater than 10 years of age. Identifying that while the FFS is decreased for those patients who did not receive RT initially, the OS is similar, the authors conclude that disease progression or relapse in those patients may be salvaged with later RT. These data differ from earlier protocols where delayed RT was associated with a worse prognosis for BP RMS; however, those inferior results were also on older chemotherapy and local control protocols. Treatment for local failure includes more aggressive chemotherapeutic regimen, in addition to RT, potentially increasing the therapy burden over what it would have been with initial RT without relapse, with the potential benefit of avoiding RT altogether. The authors suggest that there is a need to identify those who need upfront RT in order to spare those for whom its toxicity will not be of benefit.[131]

Evaluating an alternative for radical surgery and external RT for local control of BP RMS, a group in France reported results of conservative surgery (bladder neck and urethral preservation) in combination with 60 Gy brachytherapy. Twenty-six patients were treated between 1991 and 2007, with initial risk-based chemotherapy on SIOP protocols (MMT 89, 96, and 98) or European protocol RMS 2005. Patients were selected for the local treatment protocol according to response to first-line chemotherapy. Candidates included prostate tumors or those with no bladder extension above the trigone (outside field of brachytherapy), and surgical procedure was partial prostatectomy with urethral preservation or partial cystectomy of the bladder neck or trigone with extravesical ureteral reimplant, if needed. Plastic tubes for brachytherapy were implanted intraoperatively, and 60 Gy brachytherapy was delivered at a rate of 10 Gy daily. Twenty-six boys were treated with no resection considered microscopically complete, and 11 with macroscopic residual at tumor resection. Only four patients had no viable tumor, and three of them had metastatic disease. At a median follow-up of 4 years, 24/26 patients were alive, and only one of the survivors had undergone cystecomy, which was secondary to severe bladder dysfunction and associated hydroureteronephrosis. One patient with bone and nodal relapse responded to chemotherapy. One death was related to pulmonary relapse, and the other relapsed locally, outside the brachytherapy field, as well as in the lungs. Local treatment complications included rectal bleeding that resolved spontaneously, recurrent bladder stones in one patient, and ureteral stenosis treated with short-term stenting in another. Continence results are reported for 18 boys older than 4 years, and 15 demonstrated normal daytime continence responsive to anticholinergics and bladder education. The authors postulate that given that there was no relapse in the field of brachytherapy, even in the presence of gross residual disease, consideration may be given to biopsy alone, followed by brachytherapy for local control of RMS of the prostate and bladder neck.[164]

Female Genital Tract

From 1972 to 1996, with the advent of effective chemotherapeutic regimens, the rate of surgical tumor resection for vaginal or uterine RMS decreased from 100% to 13%. Management with chemotherapy and restrictive surgery has demonstrated excellent long-term survival and frequent uterine preservation. Arndt et al. reviewed the 151 patients with RMS of the female genital tract out of the 4272 RMS patients enrolled in IRS I–IV. The 5-year OS was 82%. Chemotherapy was primarily VAC based. Local control was surgery alone in 42%, surgery and RT in 19%, biopsy and RT in 12%, and biopsy without RT in 21% (no local therapy). Many with primary vaginal tumors received delayed RT or had it omitted

with excellent outcome. Hysterectomy rates decreased from 48% in IRS I or II to 22% in IRS III or IV, with an increase in RT from 23% in IRS II to 45% in IRS IV. There was no significant difference in survival over the course of the four trials for patients with localized embryonal or botryoid tumors. Prognostic factors included improved prognosis for ages 1–9, embryonal histology, N0 disease, noninvasive tumors, and the use of IRS III or IV treatment protocols. Patients outside of the 1- to 9-year age range particularly benefited from the intensified treatment of IRS III or IV (5-year survival 67% IRS I or II vs. 90% IRS III or IV). Treatment toxicity was the cause of 43% of deaths in patients with group I–III tumors. Unlike RMS at other sites, in this subgroup of patients, 67% of those who developed recurrent disease were salvaged with multimodal treatment, including chemotherapy, surgery, and RT, if not previously received. The authors recommended continued use of primary chemotherapy of VA for group I or II eRMS and VAC for group III disease, with individualized local treatment plans based on tumor site and histology. Those with nonembryonal female genital tract RMS should receive intensified chemotherapy, as they are of intermediate recurrence risk. Delayed RT is recommended for selected patients, such as those with positive margins after chemotherapy and local surgery, those with vulvar eRMS group II or III tumors, and all those with eRMS who are lymph node positive.[165] Subsequent elimination of RT and cyclophosphamide from treatment of vaginal eRMS in COG D9602 (1997–2004) resulted in a reduction of local control rate to 50% from 14% and 7% from IRS III and IRS IV. Therefore, future study mandates include RT for girls with group II or III vaginal tumors and evaluation of a low-dose cyclophosphamide to decrease chemotoxicity while maintaining efficacy.[147]

The COG enrolled low-risk eRMS patients in ARST0331 starting in 2004 with a protocol similar to that of D9602, with a slight delay in RT and utilization of a lower-dose cyclophosphamide in patients with nonresected localized vaginal RMS than in D9602. A high rate of local recurrences, primarily in the group III vaginal tumor patients, resulted in the suspension of enrollment in these studies for stage 1/group III and stage 3/group I or II vaginal RMS patients in these protocols. Between the studies, 41 patients with localized vaginal RMS were enrolled in 1997–2008. Primary site disease progression occurred in four group IIA or III N0 prior to local therapy and in 8/31 patients with group IIIA or III N0 who completed protocol therapy, in addition to 1/2 group I patients who developed disease progression during protocol therapy. The 5-year local recurrence rate for group IIA or III N0 vaginal RMS was 26%, and the 2-year local recurrence rate was 43% for group III N0 vaginal RMS in ARST0331. These results compared unfavorably both for the local recurrence rate on the same study for group IIA or III N0 at sites other than vagina (14%) and for similar patients on IRS III or IV (5-year FFS of 83%). These poorer outcomes were attributed to the delay or avoidance of RT in patients with unresected vaginal RMS who received low-dose or no cyclophosphamide. While local control was worse than at prior series, the OS was excellent with intensified chemotherapy, radical surgery, and RT. Identification of these differences has resulted in amending ARST0331 to include RT in the local therapy of girls with group II or III vaginal RMS, with the permitted omission of RT for children less than 24 months if potential toxicity is considered unacceptable. (https://www.ncbi.nlm.nih.gov/pubmed/21298768)

Late Effects of Therapy

Because of the improved long-term survival and the use of intensified chemotherapeutic regimens, several serious and potentially life-threatening therapy-related complications have emerged. In IRS IV pilot studies, the incorporation of ifosfamide into front-line therapeutic protocols for children with unresectable tumors was associated with a 14% incidence of renal toxicity. Factors that contributed to that toxicity included high doses of ifosfamide (>72 g/m^2), age younger than 3 years, and preexisting renal abnormalities, such as hydronephrosis. https://www.ncbi.nlm.nih.gov/pubmed/1548524; https://www.ncbi.nlm.nih.gov/pubmed/8157032. Toxicities for the final IRS IV trial included greater than 90% myelosuppression, 55% severe infections, and only 2% severe renal toxicity. Toxic deaths were highest in the VAC regimen in patients with preexisting renal abnormalities (3/56), with rates for other regimens less than 1% (neutropenia with septicemia = 6, metabolic = 1, and other = 1).[113]

Of the 109 patients with BP tumors who were treated in IRS I and II, 29% developed posttherapy hematuria, 29% showed evidence of delayed pubertal development, and 10% had growth retardation.[161]

The occurrence of second malignant neoplasms is one of the most devastating sequelae of successful contemporary therapy. Of the 1770 patients enrolled in IRS I and II, 22 developed second malignant neoplasms (10-year cumulative incidence rate of 1.7%). The most common malignancies were bone sarcomas ($n = 11$) and acute nonlymphoblastic leukemia ($n = 5$). The median time to development of these neoplasms was 7 and 4 years, respectively.[166] In the IRS III trial, acute myeloid leukemia occurred in 5 of the 1062 patients enrolled. All the patients received the alkylating agent cyclophosphamide, and four received etoposide. The median time to development of acute myeloid leukemia was 39 months; median follow-up was 3.7 years.[167] IRS IV had 10 second malignancies in the initial report (myelodysplastic syndrome or acute myeloid leukemia = 4, acute lymphoid leukemia = 1, lymphoblastic lymphoma = 1, osteogenic sarcoma = 1, leiomyosarcoma = 1, undifferentiated sarcoma = 1, and primitive neuroectodermal tumor = 1) for a 3-year cumulative risk in locoregional disease on IRS IV of 2%.[113] A large review of secondary malignancies in long-term survivors of childhood RMS was performed by Scaradavou et al.[168] They reported on 130 patients with a median follow-up of 9 years. Seven patients (5.4%) developed secondary malignancies, including three with acute nonlymphoblastic leukemia and four with solid tumors. This study identified an increased risk of secondary neoplasms in patients receiving the chemotherapeutic agents carmustine and doxorubicin. They did not find RT to be a significant risk factor, in contrast to the findings from the Late Effect Study Group, which reported an increased incidence of secondary neoplasms within prior radiation

fields. Additionally, there are case reports in the literature of other secondary malignancies after RMS treatment, including adenocarcinoma of the colon associated with radiation colitis 13 years after treatment for bladder RMS, bladder transitional cell carcinoma 8 years after cyclophosphamide for eRMS, and Hodgkin's disease after childhood RMS therapy.[169]

A recent long-term evaluation (23-year median follow-up) of the Italian Cooperative Study RMS 79 (1979–1987) identified 6/163 patients who developed second malignant tumors, with 2 of those patients dying from the secondary malignancy. RMS was a GU primary in three patients with secondary malignancies of rectal carcinoma, angiosarcoma of the heart, and breast carcinoma after primary vaginal, bladder, and bladder RMS, respectively. Factors predictive of late events (second malignancy, late recurrence, and treatment-related effects) included tumor site and IRS group.[128]

Residual Disease

Even with a good histological tumor response to chemotherapy, a residual mass may retain a large amount of stromal tissue and residual mass dimensions may not be indicative of cancer burden.[102] FDG-PET and CT scan are useful for staging RMS. Dharmarajan et al. evaluated serial PET/CT for correlation with local control by imaging at baseline, just prior to radiation, and after RT. The median SUV of the primary site in 58 patients with evaluable data at baseline was 7.0, and the authors identified that complete resolution of abnormal FDG-PET uptake is predictive of local relapse-free survival across all stages, clinical groups, sites, and histologic subtypes.[170] COG protocol ARST0531 for intermediate-risk RMS will be evaluating serial FDG-PET uptake values at weeks 1, 4, and 15 of treatment and correlating them with FFS.

Recurrence

Review of IRS I–III for group I patients found 86/439 patients relapsed with a median follow-up of 12.9 years for IRS I, 9.1 years for IRS II, and 4.6 years for IRS III. Relapses in these patients occurred within 1 year in 48% and 3 years in 93%, while two patients relapsed as late as 10 years after diagnosis.[135] In IRS III, the estimated 5-year cumulative incidence of local failure was 19%, the regional nodal recurrence was 2%, and the distant recurrence was 11%. Lymph node involvement at diagnosis was the single factor most predictive of increased total local failure risk (5-year cumulative incidence of 32%) compared with children with negative nodes or unknown node status (16%). The 5-year FFS and OS rates were 70% and 78%, respectively.[171]

IRS IV had a 3-year estimated cumulative incidence of local, regional, and distant failures of 10%, 4%, and 7%, respectively.[113] Retrospective analysis of survival for 605 patients after relapse in IRS III and IV revealed that 5-year survival depended significantly on histology (64% of botryoid, 26% of embryonal, and 5% of alveolar). eRMS stage and group at presentation affected the probability of relapse survival (52% stage 1/group I and 12% stage 4/group IV), but the type of relapse was only influential in initial stage 1/group I disease, with survival for local relapse 72% and distant relapse 30%. Relapse in aRMS was associated with better survival after an initial group I tumor compared with other initial presentations, despite location of recurrence (40% vs. 3%).[172]

From the IRS trials III, IV pilot, and IV, the estimated 10-year late-event (disease recurrence, second malignant neoplasm, or death from other causes) rate was estimated at 9%. The estimated cumulative incidences of the specific subtypes of failures at 5 and 10 years were 2.4% and 2.7% for recurrence, 1.9% and 2.4% for second malignant neoplasms, and 0.8% and 3.5% for death as a first event. Patients with both advanced disease (groups III and IV) and large primary tumors at diagnosis (>5 cm) were at the highest risk for late events. The probability of a late event in the high-risk group of patients was 19%.[173]

Bisogno et al. completed a long-term review of 163 patients enrolled in RMS; 79 were treated with cyclophosphamide, adriamycin, and vincristine (CAV) alternating with VAC. Patients with group II or greater tumors at presentation were eligible for RT. At a median follow-up of 23 years, 83 patients were alive with no evidence of disease. Forty patients had experienced a tumor recurrence at less than 3 years, with an additional eight recurrences at greater than 3 years, and two of those at greater than 5 years (8.6 and 8.7 years). Most of the late (>3 year) relapses (seven) were local, while one patient had a combined metastatic and local relapse, and only one of the seven relapsers who demonstrated a second complete treatment response was alive at 22 years after the event. The poor prognosis for late relapse (more than 3 years after initial diagnosis) is different than that for other shorter-term studies, which identified that prognosis improved with recurrence further removed from treatment completion. The additional late relapses increase the recurrence rate to 29% with long-term follow-up.[128]

Relapse in aRMS continues to have a dismal clinical outcome, prompting ongoing evaluation of novel therapies. Dagher et al. evaluated the effectiveness and toxicity of a peptide-pulsed vaccination targeting the break point region of fusion proteins administered concomitantly with continuous interleukin-2 (IL-2) infusion. Treatment did not alter the poor outcome for all 16 translocation-positive Ewing's sarcoma and aRMS patients, who continued to have progressive disease after immunization. All patients in this trial were significantly immunocompromised and had large, bulky tumors.[174]

Ninety-two patients with measureable disease and unfavorable prognosis at relapse (initial diagnosis of aRMS, stage 1/group I eRMS with distant recurrence, or initial diagnosis of eRMS stage 2 or greater/group II or greater) were enrolled in COG protocol ARST0121 (2002–2006) and randomized in a phase II window trial of irinotecan and vincristine to one of two treatment schedules (prolonged or short). The treatment resulted in a 32% overall response rate with no significant difference between the two regimens, and no improvement over historical reports.[119]

In a review of their results in the treatment of recurrent RMS, Hayes-Jordan et al. identified that 37% of patients who underwent surgical resection of recurrent disease were alive with no evidence of disease at a mean follow-up period of 4.9 years after surgery, and recommend that aggressive surgical resection of recurrent disease is warranted.[175]

Investigational

Differentiation therapy is a novel approach for cancer treatment in which the principle is to transform malignant cells into mature cells and decreases side effects of classical chemotherapy, such as drug resistance and cytotoxicity. This technique has shown in vitro effectiveness utilizing GR-891 and QF-3602 (5-fluorouracil acyclonucleoside derivatives) against RMS cell lines by inducing terminal myogenic differentiation with no cytotoxicity, increased adhesion capability, and no induction of MDR1, a gene that induces multidrug resistance.[176,177] Muscle-specific microRNAs miR-1 and miR-206 have been identified as potential promoters of muscle differentiation with low expression in RMS cells. Additionally, when RMS cells were exposed to a differentiation medium, miR-1 and miR-206 were not induced, and the reintroduction of miR-1 and miR-206 to RMS cells promoted myogenic differentiation.[178]

Antiangiogenesis therapy is a novel treatment approach of great research interest. The angiogenesis stimulators VEGF, basic fibroblast growth factor, and IL-8 all have been identified as products of eRMS, and effective antiangiogenic therapies may require multiple drugs to target several angiogenic factors.[179–181] Landuyt et al. induced tumor necrosis in subcutaneous RMS in rats using the angiogenesis inhibitor TNP-470, with both tumor volume and drug dose affecting treatment outcome and therapy found to be potentially useful to treat progressive tumor growth and large tumors.[182] Antibodies to VEGF have been shown to decrease growth of RMS cell lines; however, there is upregulation of host VEGF in response to hypoxia, indicating a need to completely block VEGF for maximum tumor inhibition.[183] VEGF and VEGFR2 (fetal liver kinase 1 [Flk-1]) play a role in tumor angiogenesis. Dc101, an anti-Flk-1 antibody in conjunction with doxorubicin, demonstrated greater antitumor activity in RMS cell lines xenografted in immunodeficient mice than doxorubicin alone.[184]

An alternative method of targeting tumor-specific vascularization is antivascular therapy, which would target inadequate and ill-structured tumor vasculature. Combretastatin A4 phosphate (CA4P) is an antivascular drug that, when administered systemically to rats, induced growth delay in solid RMS with a greater effectiveness with larger tumor volume.[185] Further investigations of CA4P have utilized this agent in a dual-targeting approach, with CA4P utilized to induce tumor necrosis and then treating with necrosis-avid I131-tagged hypericin, resulting in a radiotherapeutic response to kill residual cancer cells and inhibited tumor regrowth.[186]

PROGNOSTIC FACTORS

Presentation

Among patients with nonmetastatic RMS, multiple factors have been identified to be associated with poorer outcome, including age less than 1 year or greater than 10 years, alveolar histology, tumor size greater than 5 cm, tumor invasiveness, nodal disease, advanced clinical group, and unfavorable primary site.[101,144,187] Among those factors, age and unfavorable site, in addition to greater than or equal to two metastatic sites and bone or bone marrow involvement, have been noted to be associated with a particularly unfavorable outcome.[101,148]

Infants and Adolescents

Age has been demonstrated as a prognosticator in RMS. Specifically, ages less than 1 year and greater than 10 years have been identified to be associated with decreased EFS in metastatic[148] as well as localized[187] RMS.

In addition to poorer prognosis,[148,188] adolescents have also demonstrated less improvement in survival rates over recent years[189,190] than their younger counterparts. Joshi et al. analyzed pooled data from IRS III, IV pilot, and IV (1983–97, 2343 patients) and identified age as an independent risk factor for RMS treatment failure, with a significantly worse prognosis identified in patients less than 1 year or greater than 10 years than those age 1–10 years (5-year FFS of 53%, 51%, and 72%).[188] Bisogno et al. analyzed the results for patients enrolled in serial Associazione Italiana di Ematooncologia Pediatrica (AIEOP) Soft Tissue Sarcoma Committee protocols from 1988 to 2005 as a function of age (<15 years classified as children and 15–19 years classified as adolescents). Adolescents had a longer delay from onset of symptoms to diagnosis (median 8 vs. 4.6 weeks), more GU non-BP tumors (37% vs. 13%), an alveolar histology (47% vs. 33%), lymph node involvement (36% vs. 22%), and metastases at diagnosis (30% vs. 18%).[191] As they were enrolled in the same protocols, both age groups received similar treatments consisting of surgery, RT, and chemotherapy. However, with a median follow-up of 8.8 years, adolescents demonstrated a worse 5-year OS (57% vs. 69%, $p = 0.006$) and PFS (48% vs. 64%, $p = 0.02$) than children. When substratified for localized compared with metastatic disease, outcomes for those with localized disease were similar between the groups; however, the differences for metastatic disease were more pronounced, with adolescents demonstrating decreased OS (25% vs. 32%) and PFS (6% vs. 10%) compared with children. In addition to favorable tumor site and absence of lymphatic or metastatic disease, on multivariate analysis, an age of <15 years was an independent prognostic factor for OS and PFS.

Given the historically poorer outcomes for infants with RMS, Malempati et al. reviewed the outcomes for 76 infants (<1 year of age at diagnosis) with nonmetastatic RMS treated on IRS IV and IRS V protocols D9602 (low risk) and D9803 (intermediate risk) from 1991 to 2005 compared with 1767 children older than 1 year. Protocols recommended that infants receive initial 50% doses of chemotherapy with dose escalation if no significant toxicity resulted. RT was directed for all group II and III and aRMS patients. eRMS was the most common histology, followed by aRMS (21%), with other histologies, such as undifferentiated sarcoma and EM, comprising a minority of cases. More than half of infants had group III tumors. The local failure rate for infants was 30% compared with 13% for all patients, particularly remarkable for group III tumors, with a rate of 42% for infants compared with 17% for all group III patients. Among the infant group III tumor failures, one-third received RT and nearly two-thirds (11/18) received no local therapy. Despite worse

local control, group III RMS infants in whom RT was withheld experienced similar OS rates, suggesting that many are salvaged after local recurrence, and therapeutic options must be individualized, balancing long-term morbidity with increased rates of local failure and death.[192]

CONCLUSION

The advances in understanding the biologic and genetic features of RMS, as well as the development and scheduling of new drugs, have improved the survival of these children. However, several challenges still remain. The refinement of risk-directed therapy based on the understanding of newly recognized, biologic, and clinical features is ongoing to limit the most significant treatment toxicities to those children whose survival requires more toxic therapies. Utilization of newly developed hematopoietic growth factors will allow dose intensification, and may offer improvement in children with metastatic or recurrent disease. Genetic abnormalities, such as translocation (PAX3-FKHR and PAX7-FKHR) in some alveolar tumors, may provide molecular targets for future therapies, as well as better direct therapies based on risk stratification.

OTHER PELVIC TUMORS

While RMS is the most common pediatric bladder tumor, pediatric bladder masses may represent many other entities. A retrospective review of 98 bladder lesion specimens from 65 patients over a 21-year period was completed at the Children's Hospital of Philadelphia, confirming RMS to be the most common lesion (32 cases and 15 patients), followed by non-RMS/nonurothelial neoplasms (25 cases and 16 patients), which included most frequently fibroepithelial polyps (7 cases and 7 patients). Additional nonurothelial neoplasms included inflammatory myofibroblastic tumor, pseudosarcomatous myofibroblastic proliferation, paraganglionoma, neurofibroma, leiomyoma, leiomyosarcoma, and a necrotic spindle cell lesion. Eleven cases of urothelial neoplasm were diagnosed in 6 patients (2 patients with urothelial papilloma, 2 papillary neoplasms of low malignant potential [PUNLMPs], 1 inverted papilloma, and 1 low-grade papillary urothelial carcinoma), and the balance of cases were categorized as reactive or inflammatory (20 cases and 20 patients), malformation (2 cases and 1 patient), or normal (8 cases and 7 patients).[193] A review of the Surveillance, Epidemiology and End Results (SEER) database identified 140 cases of bladder tumors in children under 18 years of age, with the most common being PUNLMP, followed by eRMS. Of note, however, RMS (and eRMS in particular) predominated in children of <12 years of age, and urothelial tumors were more common than RMS in the 13- to 18-year age group.[194]

Urothelial Carcinoma

Urothelial carcinoma in the first two decades of life is rare, has a male predominance, and is typically a low-grade tumor that seldom recurs or progresses.[195–202] Some of these tumors occur secondary to cyclophosphamide therapy.[136,203–206] In more than 90%, the lesions are solitary. Pathologically, 80% of these tumors are grade I or papilloma, 20% are grade I or II tumors, and only 3% are invasive through the lamina propria. The recurrence rate is low (2%–5%).

Presenting symptoms include gross hematuria (80%), irritative voiding symptoms or recurrent urinary tract infections (15%), and microscopic hematuria (8%).[207] In a recent series, Fine et al. reviewed 23 patients with urothelial neoplasms presenting under 20 years of age. None had a history of cancer, family history of bladder cancer, exposure to radiation or chemotherapy, or parents with occupational exposure to bladder carcinogens. Twelve tumors were urothelial papillomas or PUNLMPs, while 11 were noninvasive urothelial carcinomas (8 low grade and 3 high grade). Among the 3/21 patients who recurred, initial pathology was papilloma, noninvasive low-grade urothelial carcinoma and PUNLMP with recurrences demonstrating benign papilloma and PUNLMP.[208]

Wild et al. analyzed urothelial tumors from 14 patients ranging in age from 4 to 19 years for FGFR3 and TP53 mutations, using comparative genomic hybridization, UroVysion fluorescent in situ hybridization (FISH) analysis, PCR for human papilloma virus, and LOH for chromosomes 9p, 9q, and 17p. Genetic alterations that are frequent in adult urothelial carcinomas were rare in this pediatric cohort, and the author concluded that pediatric urothelial neoplasms appear to be biologically distinct from adult counterparts, lacking in most cases genetic instability.[209]

Recurrent urothelial carcinoma has been reported in association with Costello syndrome, a rare autosomal dominant condition that has also been associated with eRMS. Hematuria in a patient with Costello syndrome warrants evaluation for a bladder tumor.[210,211]

Previously attributed to a history of radiation or cyclophosphamide exposure, patients and families with hereditary retinoblastoma demonstrate an increased incidence of urothelial carcinoma. The recognition that this predilection occurs even in a patient who has not been exposed to high-dose radiation or cyclophosphamide resulted in the conclusion that urothelial carcinoma appears to be part of the hereditary retinoblastoma spectrum.[212]

The initial diagnosis of urothelial carcinoma can be made by ultrasound, which in some series was found to be 100% sensitive. Intravenous pyelogram and CT scans may not be able to detect small tumors. Cytologic evaluation is of limited value, as most of these tumors are low grade.[196,207] Cystoscopy allows definitive diagnosis, staging, and treatment of these tumors; however, its role in surveillance of the pediatric patient remains ill defined, as it requires general anesthesia in the setting of a low risk of recurrence.

Bladder Augmentation–Related Urothelial Carcinoma

Patients with a history of bladder augmentation appear to have a predisposition to epithelial bladder tumors.[195] Soergel et al. reported three cases of urothelial carcinoma in patients at 29, 37, and 44 years of age who had undergone augmentation cystoplasty for neuropathic bladder an average of 19 years prior to presentation and did not have

any other known risk factor for development of urothelial carcinoma. Based on an assumption of a 10-year lag time for tumor development, in their series of 483 bladder augmentations, the estimated cancer risk was 1.2%. They recommend endoscopic surveillance of bladder augmentation in patients starting at 10 years after initial surgery.[213] Hamid et al. prospectively evaluated the efficacy of routine surveillance cystoscopy for patients with a history of bladder augmentation for benign disease. The protocol included annual cystoscopy for augmentation patients starting at 10 years after augmentation for 92 consecutive patients, 53 of whom consented to also undergo bladder biopsies at the time of cystoscopy. With a median follow-up of 15 years (10–33), no cancer was identified. During the period of the study, one patient who had a previously normal surveillance cystoscopy presented with intermittent hematuria and recurrent urinary tract infection and on evaluation was diagnosed with a malignancy. They conclude that routine surveillance cystoscopy in the first 15 years is not necessary, as it did not detect any cancers in their series, and did not result in early diagnosis of the one patient who did develop a malignancy. They do recommend that development of hematuria, suprapubic pain, or recurrent unexplained urinary tract infection in a patient with a history of a bladder augmentation warrants a full evaluation to assess for bladder tumor.[214]

Appanna et al. analyzed biopsy specimens from augmentation cystoplasties with comparative genomic hybridizaton and identified that genetic abnormalities were much greater in the vicinity of the enterovesical anastamosis than in areas distant to the suture line.[215] Ivil et al. identified significant chromosomal numerical abnormalities on FISH at biopsy sites from the enterovesical anastomosis of ileocystoplasty patients that did not exist in the native bladder biopsies of these patients.[216] They also identified p53 mutations at the enterovesical anastomosis in 7/38 patients, and none in the native bladder of those patients.[217] These studies all support that the enterovesical anastosmosis is a site of significant genetic instability in the presence of a bladder augmentation. This instability may result in tumor formation.

Attempting to identify a potential etiology for this evidence of genetic instability, Dixon et al. compared the effects of hyperosmolar environments on intestinal epithelial cells with those of bladder transitional epithelial cells and identified that the hyperosmolar environment inhibited activation of the DNA damage signaling and repair pathways in the intestinal epithelium, whereas these pathways were preserved in bladder transitional cells. The authors theorize that enteric epithelial exposure to urine in the case of augmentation cystoplasty may result in failure of adaptive pathways, thereby placing these tissues at an increased risk for malignant degeneration.[218]

Sung et al. evaluated the histological and immunohistochemical characteristics of four patients who presented at a mean age of 37 years with high-grade invasive urothelial carcinoma at a mean time from bladder augmentation of 19 years, and who died of disease at a mean of 5 months from diagnosis. Histologically, all tumors demonstrated brisk mitosis and tumor necrosis and demonstrated characteristic chromosomal abnormalities on UroVysion FISH analysis, identifying this as a potential surveillance strategy in patients who undergo augmentation cystoplasty.[219]

While a definitive surveillance protocol has yet to be defined, patients with a history of enterocystoplasty appear to be at increased risk for aggressive secondary tumors of the augmented bladder.

Nephrogenic Adenoma of the Bladder

Nephrogenic adenoma is a rare, benign lesion of the bladder, occurring as an epithelial response to infection, inflammation, or trauma. It presents as a papillary lesion resembling a low-grade, low-stage urothelial carcinoma.[220–223] Most children with nephrogenic adenoma will present with symptoms of gross hematuria, dysuria, and bladder instability. In a case series and literature review encompassing 21 patients, the lesion was more common in girls than boys (5:1); all patients had a history of prior bladder surgery, and 80% recurred.[220] Final diagnosis is established after cystoscopy and histopathologic review of a tumor biopsy specimen. Therapy consists of transurethral resection, long-term antibiotic therapy, and periodic cystoscopy.

Leiomyosarcoma

Leiomyosarcoma is rare in the pediatric age group and accounts for less than 2% of all soft tissue sarcomas. Diagnostic features and biological behavior in children appear similar to those in adults. The most important features in assessing malignant potential are tumor size and mitotic counts. Local excision usually provides adequate therapy.[224–227]

Urachal Adenocarcinoma

Urachal adenocarcinoma is a very rare tumor accounting for only 0.17%–0.34% of all bladder neoplasms. It usually occurs in adults, but there are several reported cases in children. This mucin-producing or colloid adenocarcinoma arises from the juxtavesical segment of the urachus and invades the bladder. The presenting symptoms may include hematuria, bladder irritative symptoms, or balls of mucous in the urine. The primary treatment is surgical resection. As its location predisposes to extensive local spread before detection and diagnosis, the prognosis is poor.[228,229]

Carcinoma of the Exstrophied Bladder

Bladder carcinoma with the history of bladder exstrophy occurs more frequently in adults than in children. It has been reported in both reconstructed and nonreconstructed bladders, as well as in patients who have undergone early cystectomy. Histologically, bladder carcinoma with a history of bladder exstrophy is most frequently reported to be adenocarcinoma; however, urothelial, squamous cell, and mixed carcinomas have also been reported.[230–242] In adenocarcinoma, the epithelial lining of the bladder is replaced with colonic epithelium with colon-specific mucin histochemistry and contents of carcinoembryonic antigen.

Mesonephric Adenocarcinoma of the Female Genital Tract

This is a rare and highly malignant tumor that can occur at any age. Approximately 30% of such tumors occur in children. Evidence that these tumors originate from the mesonephric (Wolffian) rests includes their tubular structure and their occurrence along the tract of the mesonephric duct or its remnants (vagina, cervix, uterus, and salpinx). The clinical, gross pathologic, and radiographic presentation of vaginal mesonephric carcinomas may be indistinguishable from that of eRMS. The presenting symptoms are vaginal bleeding or a vaginal mass. Radiographic features are similar to those of RMS and include grapelike clusters of tumor nodules within the vagina. Treatment includes radical excision, RT, or both.[243–246]

Clear Cell Adenocarcinoma of the Vagina or Cervix

Maternal diethylstilbestrol (DES) prior to 18 weeks' gestation has been implicated in the etiology of clear cell adenocarcinoma of the vagina or cervix. The age of the DES-exposed patients has varied from 7 to 34 years, with the highest frequency from 14 to 22 years. The risk among the exposed is in the order of 1 in 1000.[247–249] Similar to mesonephric adenocarcinoma, the presenting symptom is that of vaginal bleeding or mass. The rarity of this tumor among exposed women suggests that DES is not a complete carcinogen, but that some other factors are also involved in the pathogenesis of clear cell adenocarcinoma of the vagina and cervix.[249–256]

Cavernous Hemangiomas of the Bladder

Bladder cavernous hemangioma is a rare benign mesenchymal tumor that may present with gross hematuria and abdominal pain. In about 30% of cases, it is associated with angiomatous lesions in other parts of the body. The diagnosis may be suspected on ultrasound examination, but it is generally made at cystoscopy.[257–260] Blood pool scintigraphy using (99m)technetium–human serum albumin combined with DTPA usually reveals an area of increased activity in the bladder.[261] Biopsy and transurethral resection must be avoided because of the risk of hemorrhage. Laser treatment of hemangiomas has been reported and should be the initial management.[261] Should laser coagulation fail, partial cystectomy appears to be the most effective method of treatment.[262]

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CHAPTER 62

Exstrophy and Epispadias

Linda A. Baker and Richard W. Grady

INTRODUCTION

The exstrophic diseases, referred to collectively as the exstrophy–epispadias complex,[1] are considered a spectrum of embryological anomalies related by certain principle anatomic features. This complex includes

- *Epispadias*—The urethra is a partial or complete open plate on the dorsal surface of the phallus.
- *Classic bladder exstrophy (CBE)*—The bladder is an open plate on the low abdominal wall, and the urethra is epispadic.
- *Cloacal exstrophy (CE)*—The bladder and the ileocecal junction of the bowel are an open plate on the low abdominal wall associated with other malformations.
- *Exstrophy variants*—Partial manifestations are seen of the above malformations.

Formal historical descriptions of exstrophy date back to at least 1597, with Sherk von Grafenberg's description of this congenital defect; possible depictions of exstrophy also exist on Assyrian tablets from 2000 BC. Chaussier first coined the term *exstrophie* to describe this defect in 1780, following detailed descriptions of it by Mowat in 1748. CBE is typically a nonlethal defect at birth; further, its natural history is known and has been well described in untreated adults. Since the nineteenth century, various efforts to manage exstrophy have been described. Because exstrophic conditions are rare, these approaches were empiric and often unsuccessful. Until the twentieth century, no effective surgical remedy was available to consistently ameliorate the morbidity associated with CBE.

As we enter a second century of surgical care of the child affected by CBE, epispadias, or CE, a review of this history shows that great strides in management have been made. These anomalies are some of the most complex that pediatric urologists manage at birth, childhood, and adulthood. As well, caregivers of these patients with lifelong health issues continue to experience significant stress.[2] Clearly, significant challenges remain at every step, including the formidable process of transitioning these complex patients to adult urologists with expertise in genitourinary congenitalism.[3]

ANATOMIC PATHOLOGY

Classic Bladder Exstrophy

Brock and O'Neill describe exstrophy as "if one blade of a pair of scissors were passed through the urethra of a normal person; the other blade were used to cut through the skin, abdominal wall, anterior wall of the bladder and urethra, and the symphysis pubis; and the cut edges were then folded laterally as if the pages of a book were being opened"[4] (Figure 62.1). CBE and epispadias are not typically associated with anomalies in other organ systems away from the vicinity of the exstrophy, and these children are typically intellectually normal. However, the genitourinary tract and adjacent bony and soft tissue body parts are altered, suggesting either an epithelial or mesodermal defect in the pathogenesis.

Bladder

Anatomic features of bladder exstrophy include the anterior abdominal wall defect containing the exposed urothelium of the small nonspherical open bladder in the mons and infraumbilical regions. The umbilical stalk is at the upper edge of the bladder plate and is characteristically low in position relative to the iliac crests. The bladder plate can be large and evert with Valsalva—this would indicate a favorable bladder plate for reconstruction. The small rigid bladder plates are worrisome even before surgery. At birth, the exstrophic urothelium can be normal in appearance. However, ectopic bowel mucosa or polypoid lesions consistent with cystitis cystica and/or glandularis may be present. If left untreated and without meticulous protection after birth, the exposed urothelium will undergo squamous metaplasia in response to acute and chronic inflammation. Other inflammatory changes, such as cystitis cystica and/or glandularis, will also be seen.[5] When left chronically exposed to the environment, the areas of squamous metaplasia often undergo malignant degeneration to adenocarcinoma or squamous cell carcinoma, which can be a cause of early death.[6–12] The exstrophy detrusor has similar muscarinic receptor density and binding affinity as controls,[13] fewer myelinated nerve fibers than controls,[14] and overexpression of inflammatory genes and underexpression of developmental genes, suggesting detrusor "immaturity" on expression microarray

FIGURE 62.1 Newborn boy with classic bladder exstrophy. Note evidence of anterior placement of the bladder and epispadic urethra.

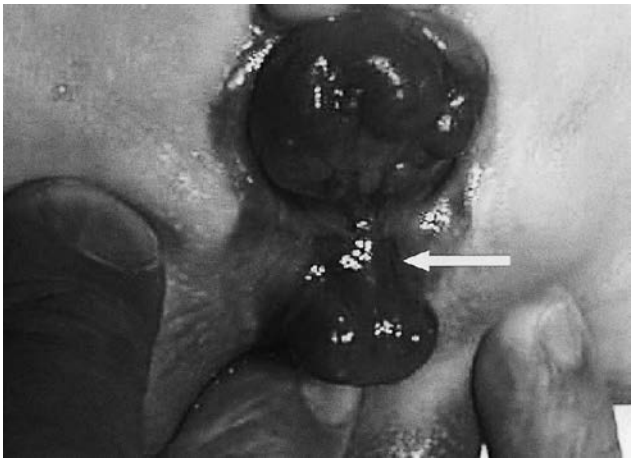

FIGURE 62.2 Newborn boy with classic bladder exstrophy. The phallus is pulled downward. The white arrow indicates the posterior urethra and location of verumontanum.

analysis.[15] Alterations in specific signaling pathways have been noted, which may contribute to the etiology (see the "Theories of Pathogenesis of Exstrophy" section).

Kidneys and Upper Urinary Tract

At birth, renal anomalies can occur with bladder exstrophy but do not occur at increased frequency and are not characteristic. Reported renal abnormalities include cystic dysplasia, ureteropelvic junction obstruction, pelvic kidney, megaureter, renal hypoplasia, and horseshoe kidney.[16] In contrast, the ureterovesical junction is abnormal in essentially all with CBE; vesicoureteral reflux is universally present after exstrophy closure due to the minimal ureteral intramural tunnel and inferior approach of the ureters into the bladder trigone from the abnormally deep pouch of Douglas.

Genitalia

Males

In CBE newborns, the misshapen penis sits at the immediate base of the extrophic bladder plate with an open urethral plate extending from the bladder plate to the glans on the dorsal penile side. The penis is deflected dorsally and may have true intrinsic dorsal chordee or urethral tethering (Figure 62.2). The foreskin is dorsally absent but sizable and hooded ventrolaterally. The glans is bivalved, being flattened and splayed by the dorsally positioned urethral plate. The penis is broad and variably foreshortened because of the varying degree of diastasis associated with exstrophy. The corpora cavernosa are proximally splayed laterally due to the pubic diastasis since each crus remains normally attached to the distracted ischiopubic rami bones. Further, magnetic resonance imaging (MRI) studies of the penile length of adult male exstrophy and epispadias patients reveal that the total corporal length is significantly shorter than in a control population. This corporal shortening apparently results from a foreshortened anterior segment (distal to the pelvic attachment); the posterior corporal segment is unaffected in exstrophy patients (Figure 62.3).[17] It has been anecdotally noted that the length of the penis and the size of the exstrophic bladder plate are inversely related.

The short urethral plate and dorsal penile curvature cause the glans penis to lie in close approximation to the prostatic veru montanum. The ejaculatory ducts empty at the veru exposed on the urethral plate. The vas and ejaculatory ducts are probably unaffected in classic exstrophy unless iatrogenically damaged.[18] Innervation to the penis is also preserved. The cavernosal nerves are located on the lateral aspects of the corporal bodies. In the normal situation, these nerves can be found on the dorsal aspect of the penis after they traverse the posterolateral aspects of the prostate and the membranous urethra.[19] At birth, the volumetrically normal prostate does not encircle the urethra but is posterior to it and is wide and flat in exstrophy.[20,21] There is an increased distance between the base of the penile shaft and the scrotum, covered by smooth skin. The scrotum is basically well formed but characteristically is broad, with its rugations oriented at a ~45° angle to the midline raphe instead of the usual horizontal lie. The testes may be retractile, undescended, or descended, and inguinal hernias are present in up to 86%, necessitating repair at birth.[22] Because of the underlying bladder neck anomalies and lack of muscular support of the posterior urethra, exstrophic males may have impaired fertility. A particular problem is retrograde ejaculation if the

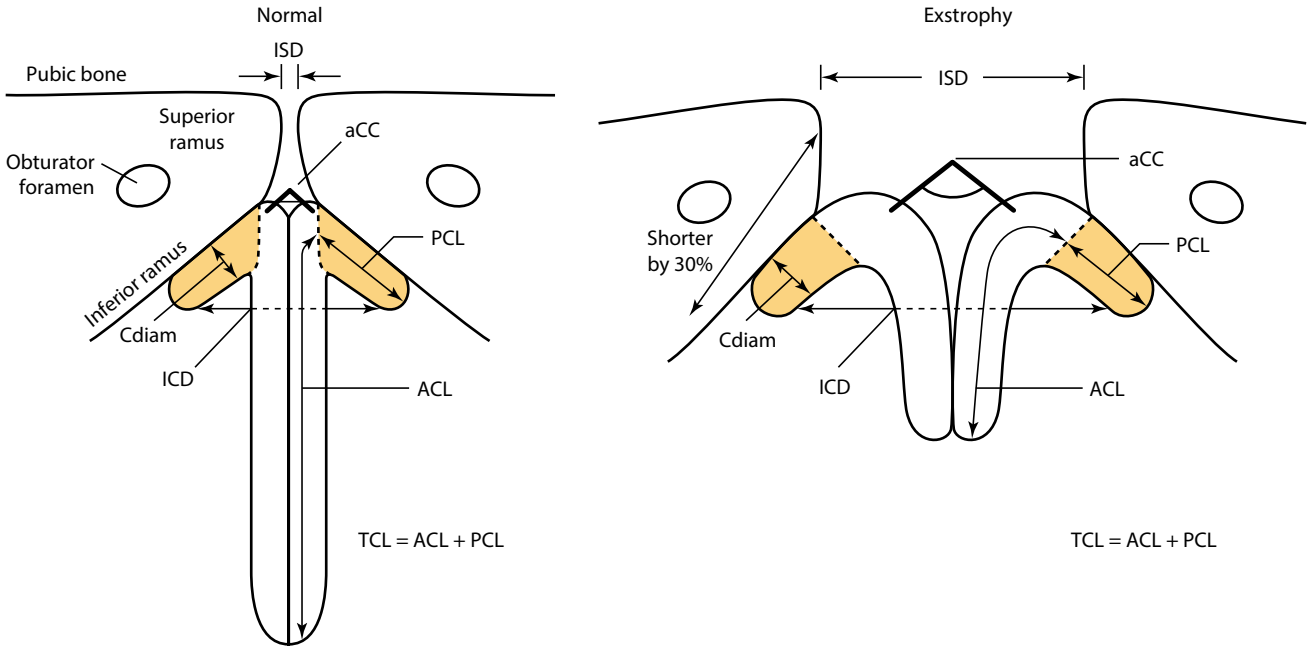

FIGURE 62.3 Penile and pelvic measurements in normal men and patients with exstrophy. ISD, intersymphyseal distance; aCC, corpora cavernosa subtended angle; Cdiam, corpus cavernosum diameter; PCL, posterior corporeal length; ICD, intercorporeal distance; ACL, anterior corporeal length; TCL, total corporeal length.[9]

bladder neck does not close completely following bladder reconstruction.[23–25]

Females

In CBE cases, the mons pubis is absent, with the centrally depressed bladder plate leading to the epispadic urethral meatus (Figure 62.4) that separates the bifid hemiclitori and split clitoral hood. The anteriorly splayed labia majora are laterally displaced. The urethral meatus is not vertically slit-like but is often horizontal, striped, and gaping. The vagina and introitus are also displaced anteriorly from their usual position. The vaginal opening may be congenitally or postsurgically stenotic in these patients, but postpubertally, the vagina tends to be J shaped, hooking ventrally with a long perineal body. Internal female genital structures (uterus, cervix, fallopian tubes, and ovaries) are typically normal in girls with CBE. Uterine or vaginal wall prolapse due to deficient pelvic floor support has been observed in up to 38% of older exstrophy patients and poses particular problems with pregnancy.[26–28] Early primary bladder reconstruction with pelvic closure may decrease this risk, but this is debated.[29] A uterine suspension procedures such as sacrocolpopexy can be employed in these situations as well with pelvic osteotomy.[30]

FIGURE 62.4 Female epispadias in a 5-year-old. Chronic perineal skin changes are due to lifelong frank urinary incontinence. Note the depressed mons pubis, bifid clitoris, outwardly rotated labia minora, and open gaping urethral meatus just above the vaginal introitus.

Anorectal and Intestinal Abnormalities

The anus is often located anteriorly in CBE. Surgical procedures involving these patients should preserve the anal sphincter mechanism. However, some exstrophic patients will have insufficient anal continence due to the underlying abnormalities of the pelvic floor support structures, including the levator ani and puborectalis muscles. Anal sphincter weakness not only impacts fecal continence but also limits the use of ureterosigmoidostomy and its

FIGURE 62.5 Plain abdominal radiograph demonstrating pubic diastasis in a patient with bladder exstrophy.

variants, i.e., rectal bladder, ileocecal ureterosigmoidostomy, etc. In untreated patients, rectal prolapse also can occur due to insufficient pelvic floor support. This is usually definitively treated with formal exstrophy repair that corrects the lack of anterior pelvic support. In the interim, most rectal prolapse is intermittent and reducible.[31,32]

Skeletal Abnormalities

Diastasis of the pubic symphysis occurs as part of the exstrophy complex (Figure 62.5). This results from outward rotation of the innominate bones along both sacroiliac joints. Outward rotation of the pubic rami at the iliac and ischial junctions is seen as well. Sponseller et al. have quanitfied the differences in the pelvic anatomy of patients with exstrophy, noting (1) a 12° external rotation of the innominate bones on the sagittal axis, (2) retroversion of the acetabula, (3) an increased distance between the left and right triradiate cartilage, (4) 18° external rotation and shortening (by 30%) of the anterior segment of the iliac bone, and (5) external rotation of the posterior segment of the ileum (Figure 62.6).[33] These pelvic bone abnormalities contribute to splaying of the penis noted with exstrophy and epispadias and cause the penis to appear foreshortened. Sixteen percent will have developmental dysplasia of the hip.[34] Gait abnormalities in these children arise as a consequence of these bone abnormalities. Many of these children learn to ambulate with a wide waddling gait. This gait abnormality resolves as the children grow, most without long-term hip sequelae.[35] Orthopedic procedures to reapproximate the pubis symphysis do not appear to offer any long-term benefits to these patients from an orthopedic viewpoint. Osteotomies to reapproximate the pubis symphysis do, however, increase the chance of successful primary bladder closure in selected patients and may have a significant role in securing continence and support of the pelvic diaphragm and female internal genitalia.[30,36,37]

Fascial Abnormalities

Fascial abnormalities include the rectus fascial deficit associated with the exposed bladder. Inferiorly, the pelvic floor support structures are also compromised, which in females contributes to the uterine prolapse. At the inferior portion of the fascial defect, these patients possess an anteriorly located intersymphyseal ligament or band representing the attenuated urogenital diaphragm. The rectus muscles diverge laterally with the widened pubis symphysis. This abdominal defect is most severe in CE. Umbilical hernias also uniformly occur with exstrophy and are repaired at the time of the primary repair. An omphalocele can also be found in association with CBE, although this is rare.[38]

As previously discussed, inguinal hernias are commonly associated with exstrophy in both male and female patients (Figure 62.7).[39,40] The majority are indirect hernias. They likely occur as a consequence of the enlarged internal and external inguinal rings noted in these patients in conjunction with compromised fascial support and lack

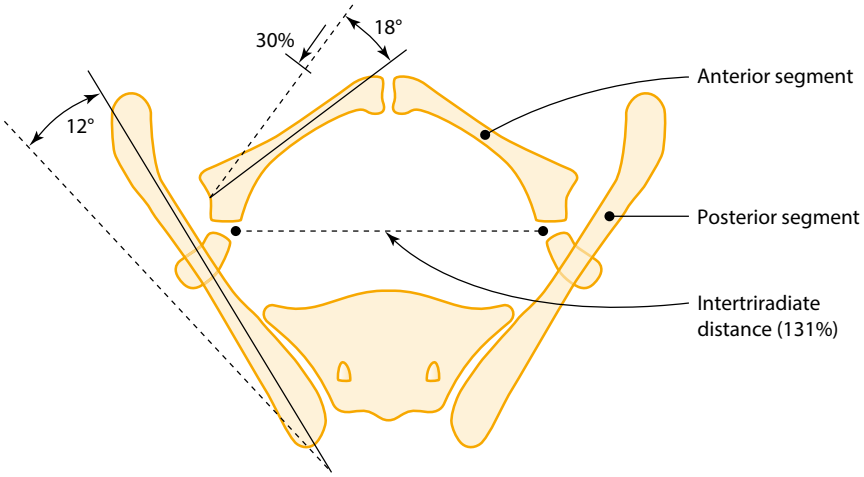

FIGURE 62.6 The anatomy of the normal bony pelvis is seen in transverse view. Superimposed are the deviations observed in the pelvis of classic bladder exstrophy patients. In the posterior segment, each half is externally rotated 12°. The acetabulae are retroverted, yielding an increased intertriradiate distance. In the anterior segment, each half is externally rotated 18° and is on average 30% shorter.[18]

FIGURE 62.7 Evidence of an inguinal hernia in this newborn male with bladder exstrophy, as demonstrated by the inguinal bulge.

of obliquity of the inguinal canal.[41,42] As several series have found inguinal hernias in up to 85% of patients, with cases of incarceration during the exstrophy closure recovery, it is recommended that these hernias be repaired at the time of primary bladder closure.[22,43] Reinforcement of the transversalis and internal oblique fascia during hernia repair decreases the incidence of later direct inguinal hernias.

Neurologic System

Spinal cord abnormalities are the exception rather than the rule in CBE. Occult spina bifida and even myelomeningocele can be seen in combination with bladder exstrophy, but this is a rare occurrence.[44]

Cloacal Exstrophy

CE, also known as the OEIS (omphalocele, exstrophy of the bladder, imperforate anus, and spinal defects) complex is a multisystem malformation. In contrast to CBE, patients with CE uniformly have associated anomalies outside of the genitourinary system and adjacent soft tissues.[45,46] These anomalies can affect the upper urinary tract, gastrointestinal tract, skeletal system, and neurologic system.

Bladder and Hindgut Plate

The bladder plate associated with CE is divided in half by the hindgut plate; the hindgut plate represents the deformation in the development of the colon that occurs with CE. Ileum enters and intussuscepts into the middle of the hindgut, creating the "trunk of an elephant's face" appearance, with appendiceal appendages located laterally to give the impression of "tusks on the face of the elephant" (Figure 62.8).[47]

With CE, the bladder neck (internal urethral sphincter) and external urethral sphincter are not fully developed due to the failed development of the bladder and urethral remnant located on the anterior and dorsal surfaces of the

FIGURE 62.8 Newborn male with cloacal exstrophy. The omphalocele is small. The terminal ileum is intussusepted and is the long 'trunk' to the patient's left. Each hemipenis is small, the left being smaller than the right.

body wall and penis, respectively. However, because the innervation to these structures is usually intact, anatomic closure theoretically offers the possibility of achieving urinary continence.[13,26,48] This may depend, however, on the status of the spinal cord. The urethral plate is characteristically short as well.

Kidneys and Upper Urinary Tract

Renal anomalies are much more common with CE. They include anomalies of location, such as pelvic kidneys or crossed fused ectopia. Horseshoe kidneys, renal agenesis, and ureteropelvic junction obstruction may occur as well.[26]

Genitalia

At birth, some may be confused as to the sex of the infant, as the genitalia are quite distorted. The exstrophic tissue may bulge downward over the penis or clitoris, but these structures can be seen when this is lifted up. Even though laterally displaced, typically the scrotum is rugated and baggier than the smooth tight labia majora.

In CE, the penis is often completely separated into two hemiphalluses due to the wide pubic diastasis, and they may not be equal in size (Figure 62.8). This can make subsequent reconstructive efforts technically more challenging if a male phenotype is preserved. Cryptorchidism is the rule with CE. The scrotum may be fused or bifid with significant ectopy.

For girls, in addition to the genital pathology described above with bladder exstrophy, uterus didelphys and other fusion anomalies of the Müllerian duct structures are seen in up to two-thirds of CE patients. Vaginal agenesis occurs in a third of girls with CE. The internal and external female genital anatomy should be defined at the time of early surgeries, as incomplete delineation can lead to postpubertal hematometrocolpos, which typically necessitates yet another surgical intervention.

Gastrointestinal Abnormalities

Associated intestinal abnormalities specific to CE include imperforate anus, foreshortening of the midgut, bowel duplication, malrotation, intestinal atresia, and Meckel's diverticulum.[26] These are in addition to the exstrophy of hindgut, ileal intussusception, and exposed appendices that are considered part of the primary pathology of CE. In cases with large omphalocele, the liver can herniate.

Skeletal Abnormalities

In addition to the features seen with bladder exstrophy, up to 50% of patients with CE can have other skeletal abnormalities. Anomalies include vertebral anomalies, congenital hip dislocation, talipes equinovarus, and a variety of limb deficiencies.[33]

Fascial Abnormalities

The fascial anomalies associated with CE include those described above for bladder exstrophy. Further, omphaloceles often occur in association with CE.[49,50] These can be closed during the initial bladder closure if they are small. If the omphalocele is large, it may require closure as a primary procedure, with the reapproximated bladder halves acting as a silo to decompress intra-abdominal pressure. Alternatively, omphaloceles may be treated with antiseptic paint to promote skin overgrowth. Our preference is to proceed with a staged surgical omphalocele correction, with primary reconstruction of the bladder at a later date if the infant is a surgical candidate. In our experience, intra-abdominal pressure following omphalocele closure determines whether we may proceed with primary bladder closure at the same time as the omphalocele repair or whether these operations must be staged. Aggressive one-stage closure of a CE can lead to organ ischemia from increased intra-abdominal pressure (abdominal compartment syndrome). Rupture of an omphalocele clearly requires immediate attention in these patients and would take precedence over other considerations. Fortunately, this rarely occurs.

Neurologic Abnormalities

Neurologic involvement of the lower spinal cord in the CE population is reported to occur in 50%–100% of patients.[50–52] Most patients have lumbar or sacral cord involvement, but thoracic-level myelodysplasia has been reported.[50] Management of CE in these situations must be coordinated with neurosurgical plans to close the neural tube defect. In addition, one-third of CE patients have an intracranial anomaly, such as hydrocephalus, Chiari, or another anomaly, warranting screening, especially in CE patients with a spinal dysraphism.[53]

Epispadias

Epispadias can be considered the least severe form of exstrophy. It does not involve the body of the bladder. However, in males, the urethra is represented as a plate of tissue located dorsally on the penis (Figure 62.9). The genital anomalies described above are noted with epispadias.

FIGURE 62.9 Penopubic epispadias in a 3-month-old male. Skin demarcation is due to chronic urine contact dermatitis in this patient.

These include lateral splaying of the penis and dorsal chordee in boys. In affected girls, the clitoris is bifid, the perineal body is broadened, and the vagina is anterior to its orthotopic or typical position (Figure 62.4). Widening of the pubic diastasis occurs as well. Importantly, the bladder neck is also frequently involved—it is often wide and incompetent. This directly affects the continence mechanism, bladder cycling and growth, and the ability to achieve urinary continence. In boys with epispadias, primary continence is possible if the epispadias is located distally and the bladder neck is normally formed. In girls, however, continence is invariably affected to some degree because of the associated urethral and bladder neck ectasia. Because the features of epispadias are shared with bladder exstrophy, clinicians consider these anomalies as part of a spectrum of the exstrophy–epispadias complex.

Exstrophy Variants

In the exstrophy–epispadias complex, variations in bladder plate size and compliance are commonplace, but no system to quantify these differences is currently in use. Phallic size and degree of phallic separation also vary from patient to patient. However, despite these variations the underlying features of this disease are consistent for classic forms of the exstrophy complex.

In contrast, patients with exstrophy variants have some, but not all, of the typical features of bladder exstrophy or CE, as well as other features not typically associated with it. These variants include covered exstrophy and superior vesical fissure. Patients with exstrophy variants may have anatomically normal genitalia despite their bladder and colon anomalies.

Bladder exstrophy variants include patients whose anatomic features resemble classic exstrophy in regard to the fascial and/or symphyseal defects but who do not have any significant anomaly associated with the urinary tract. These patients are considered to have pseudoexstrophy.[54,55] If these patients also have an isolated ectopic bowel segment in association with these findings, they are referred to as covered exstrophy variants.[56] Patients with superior

vesical fissure also have the muscular and skeletal defects associated with bladder exstrophy, but only the upper portion of the bladder is affected, so that the urethra is intact and the genitalia are less significantly affected than with classic exstrophy.[57] Duplicate exstrophy may occur. Patients with this variation have a superior vesical fissure associated with normal fascial abdominal wall development, so that components of the bladder remain ectopic, such as urothelial elements. These patients can have genital anomalies consistent with classic exstrophy as well, but this association is variable.[58–61]

CE variants also exist. These patients possess some of the features of cloacal exstophy, such as an exposed hindgut plate and bladder plate, but may not have the typical genital involvement.[62–64] Hypospadias has been described in association with CE, as well as normal genitalia, in both male and female patients. Some have been reported with intact anal innervation, permitting a Pena procedure.[65] These patients may also have other atypical features, such as accessory appendages or limb malformation. These findings, in association with prenatal ultrasound examinations that document twin gestations early in some pregnancies, suggest that aborted conjoined twinning may be the underlying cause of CE variation in some cases (Figure 62.10).[66–68]

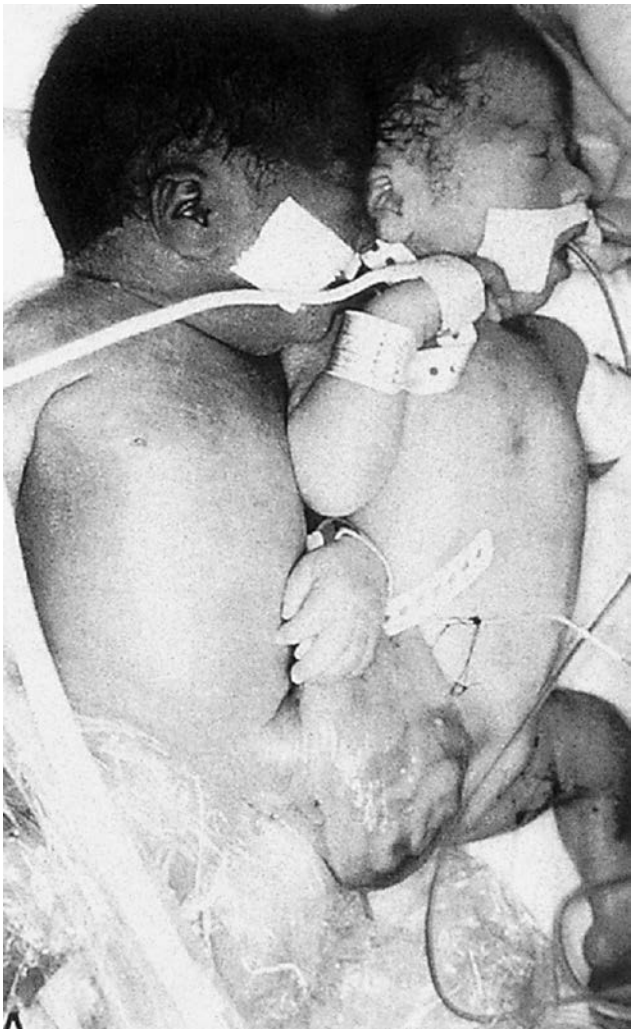

FIGURE 62.10 Conjoined twins connected by a membranous omphalocele sac containing a shared segment of distal ileum, cecum, and colon draining to a common exstrophic cloaca; an example of an exstrophy variant.

Embryology

Normal Bladder Development

Normal bladder development results in an organ that functions to store and evacuate urine. This process, known as bladder cycling, requires the bladder to store urine at low intravesical pressures during filling while maintaining continence at the level of the bladder neck. Subsequent evacuation of urine from the bladder requires a coordinated contraction of the detrusor in conjunction with relaxation of the bladder outlet. Both normal storage and emptying require intact innervation of the bladder, sphincter mechanisms, and urethra.[69]

During embryogenesis, the lateral body wall folds close the thoracic, abdominal, and pelvic portions of the ventral body wall during the fourth week of development.[70] Also, components of the urinary system, such as the ureteral buds, first appear during the fourth week of gestation. At this time, the bladder has not completely formed from the anterior urogenital sinus. Before the bladder is completely formed, mesenchyme grows inward toward the midline between the bilaminar (ectoderm and endoderm) layers of the cloacal membrane. This mesenchyme later differentiates into the abdominal wall musculature and fascia. Subsequent to this, the urorectal septum separates the bladder from the rectum by growing downward between them. Abnormalities in the appearance, timing, and function of the cloacal membrane are implicated in the creation of exstrophy. In this fashion, the urinary bladder arises during the eighth week of fetal development when the ventral portion of the urogenital sinus begins to expand.[69] With bladder filling, the mesenchymal tissue surrounding this structure differentiates into smooth muscle, which will eventually become the detrusor muscle. Ingrowth of neuronal tissue into this smooth muscle to form motor units is critical to the development of a functional bladder.[71] Embryogenesis of the pelvic floor is also important in normal fetal bladder development and function; the pelvic floor acts as a dynamic support for the bladder, which aids in both continence and volitional voiding.[72,73]

Theories of Pathogenesis of Exstrophy

CBE and CE are two of several congenital ventral body wall defects that include ectopia cordis, gastroschisis, and omphalocele.[74] Exstrophy can be considered a developmental field defect,[75] since the infraumbilical abdominal wall and genitalia react as a single unit to its perturbation in development by either a genetic mutation, environmental injury, or random factor. Improvements in our understanding of embryogenesis have led to some insight into the cause of exstrophy. In the premodern era, trauma to the unborn child or ulceration of the abdominal wall and bladder between the second and third months of life was felt to be the underlying cause of exstrophy. Through the years, many theories of embryonic morphological derangements

TABLE 62.1 Theories of embryonic morphological derangements to explain exstrophy malformation

Year	Authors	Morphological derangement
1952	Patten and Barry	Caudal positioning of primordia of the genital tubercle relative to the cloacal membrane blocks mesodermal migration
1962	Marshall	Persistence of cloacal membrane creates wedge effect, blocking mesodermal ingrowth
1964	Muecke	Abnormally large cloacal membrane blocks medial mesodermal ingrowth
1985	Thomalla et al.	Ventral hernia of the lower abdominal wall induces exstrophy
1988	Mildenberger et al.	Caudal insertion of the body stalk obstructs medial mesodermal ingrowth
1977	Beaudoin et al.	Incomplete rotation of the pelvic ring primordia
2005	Manner and Kluth	Aneurysmal dorsal aortic swellings distends the pelvis and infraumbilical abdominal wall
2005	Stephens and Hutson	Embryonic tail compresses the second sacral mesodermal stream that segments the cloacal–allantoic connection and the phallus
2008	Kulkarmi and Choudari	Cephalad origin of the genital tubercle acts as a wedge to obstruct medial mesodermal ingrowth
2011	Stec	Cellular or mechanical factors disturb mesodermal ingrowth, yielding an abnormally formed cloacal membrane that prematurely ruptures
2015	Satish Kumar et al.	Persistent pubic diastasis causes levator maldevelopment as a hammock that pushes the bladder outward and exstrophic, while the lengthening extruded midgut loop returns to the abdomen through the umbilical ring, raising intra-abdominal pressure

(Table 62.1) have been proposed that implicate an error in embryogenesis rather than an event of arrested development since the developing human embryo does not normally pass through a stage that corresponds to exstrophy.[76] The most widely supported combined theory is that abnormal cellular or mechanical factors act as a wedge, disturbing the medial mesodermal ingrowth of the body wall folds in the infraumbilical anterior abdominal wall around the cloacal membrane, yielding an abnormally formed cloacal membrane that prematurely ruptures.[73,76–80]

The bilaminar cloacal membrane, composed of endoderm and ectoderm, serves to separate the coelomic cavity from the amniotic space in early development. The cloacal membrane can first be identified during development at 2–3 weeks of gestation. By the fourth week of development, it forms the ventral wall of the urogenital sinus with the unfused primordia of the genital tubercles sitting cephalad and lateral to it. With further development, the genital primordia grow and fuse in the midline and mesoderm grows toward the midline, creating an infraumbilical abdominal wall. Simultaneous to this process, the urorectal septum develops medially and caudally to separate the cloaca into the urogenital sinus and rectum.[69] Some hypothesize that the cloacal membrane must rupture prior to 8 weeks' gestation to cause exstrophy, with earlier rupture giving CE and later rupture yielding bladder exstrophy.[75] However, evidence to the contrary is found in serial human fetal ultrasound cases of CE demonstrating late rupture of a documented intact cloacal membrane between 18 and 24 weeks.[81,82]

Animal models suggest that exstrophy results from pathophysiologic events involving the cloacal membrane. To study the persistent cloacal membrane wedge effect hypothesis, Muecke created an animal model of CE using the developing chick embryo.[358] By placing a plastic graft in the region of the tail bud, he created CE in these animals and concluded that exstrophy was due to persistence of the cloacal membrane, as Marshall had originally postulated.[76] Thomalla and coworkers developed a model of CE in the developing chick embryo by using a CO_2 laser to create an early dehiscence in the tail bud caudal to the omphalomesenteric vessels. Their results suggest that exstrophy may be caused by failure of the mesodermal ingrowth between the ectoderm and endoderm of the cloacal membrane, which later ruptures to produce exstrophy. They hypothesize that such an ischemic event could be caused by early hypoxemic infarction in the region of the tail bud, with subsequent cellular loss of the mesoderm and herniation of the developing bladder or cloaca.[78]

In 2005, a new maldevelopment theory was put forth for CE based on a suramin-exposed chick model.[83] When these chick embryos were examined at 1 or 2 days after pericardial injection of suramin, ~8% were noted to have a midline infraumbilical opening into the cloaca and allantois, abnormal leg bud abduction, a hypoplastic tail and allantois, a broad infraumbilical pelvic region, and large aneurysmal dilation of the paired dorsal aortae at the level of the leg buds. The aortic dilation is transient, resolving on the second or third day after drug exposure, but leaving maldevelopment. These authors implicate the aneurysmal paired dorsal aorta as the primary defect leading to CE in this animal model. The chick model to study bladder exstrophy has inherent limitations. Chicks normally possess a cloaca; thus, this precludes the creation of a bladder exstrophy versus a CE.

Other animal models to study bladder exstrophy have been difficult to create. Slaughenhoupt and colleagues created an exstrophy model using fetal sheep. A significant increase in the ratio of collagen to smooth muscle was noted in exstrophic versus normal control bladders ($p < 0.05$). There was no significant difference in the ratios of types I and III collagen in the two groups of sheep bladders. These histological changes are similar in part to changes seen in human bladder exstrophy tissue.[84,85] The underlying cause of human exstrophy remains in question, but recent advances in understanding the genetics may provide clues.

Incidence

Bladder exstrophy occurs at a rate of 1 per 10,000 live births to 1 per 50,000 live births.[86–89] Older studies have found this anomaly to occur more commonly in males than females, with a ratio of 3–6:1 reported in the literature,[90] while more recent work has found an equal male-to-female ratio.[88,89] CE incidence has ranged from 1 in 200,000 to 1 in 400,000 live births,[75,91] with the overall prevalence reported at 1 in 131,579 to 1 in 317,000 births.[92,93] It is higher in females and in stillborns at 1 in 10,000 to 1 in 50,000.[94]

Genetics

Genetic factors involved in exstrophy remain incompletely defined. Because of the associated physical anomalies with this condition, patients with bladder exstrophy often have to overcome significant obstacles to reproduce. Men may need to resort to assisted reproductive techniques (ARTs) (such as intracytoplasmic sperm injection[95]) because their seminal emissions drain from their ejaculatory ducts located at the base of their bladder plate, if at all. Further, sexual intercourse due to the accompanying deformity of the phallus can be difficult for some of these patients, although the majority have some capacity for satisfactory sexual relations. In the 1800s, the prevailing thought declared males with bladder exstrophy as completely impotent because of the associated deformities of the penis.[96] Women with exstrophy were (and still are) prone to uterine prolapse and miscarriage, but pregnancies have been successfully delivered vaginally or by Caesarian section. Difficulty with conception and pregnancy is still a problem today despite in vitro fertilization and careful obstetric care.[27,97] In addition, conception by ARTs has been associated with a more than eightfold increased risk of the exstrophy–epispadias complex compared with spontaneous conception (odds ratio [OR] 8.3, 95% confidence interval [CI] 4.6–15.0, $p < 0.001$).[98] The reproductive issues combined may explain, in part, why familial patterns of inheritance of exstrophy–epispadias complex are noted infrequently.

Several factors suggest a genetic basis to exstrophy: (1) a higher concordance rate among monozygotic versus dizygotic twin pairs in bladder exstrophy[99] and monozygotic and conjoined twins in CE,[80] and (2) familial recurrence has been seen in bladder exstrophy and CE. To date, about 30 familial cases of bladder exstrophy and one of CE have been reported.[100,101] Five bladder exstrophy cases of an affected parent–child pair have been reported.[100,102,103] Another 18 cases with bladder exstrophy have been reported in twin pairs.[100] In 1984, a survey of pediatric urologists and surgeons reported nine cases related to 2500 index cases of bladder exstrophy; this same series also reported on cases of twins and noted discordance in both fraternal and identical twinships.[102] In a study population of greater than 6 million births with 208 reported cases of exstrophy, no case had a family history for this anomaly.[104] Current recommendations on counseling about risk of recurrence in a sibling of a patient with exstrophy cite an estimate of 0.3%–2.3%[101,105] and a 1:70 chance of transmission to the progeny of an affected parent.[103] A Florida population-based study found multiple births had a 46% increased risk of birth defects, with bladder exstrophy being the fifth highest adjusted relative risk.[106]

Typically, bladder exstrophy is nonsyndromic. One notable syndromic exception is focal dermal hypoplasia (FDH) or Goltz syndrome (OMIM #305600), an X-linked dominant, multiorgan ectodermal dysplasia syndrome characterized by patchy atrophic or hypoplastic skin, teeth, and nails; eye anomalies; oligosyndactyly and syndactyly and split hand and foot skeletal or limb anomalies; and in some cases, ventral body wall fusion anomalies (pubic diastasis, omphalocele, bladder exstrophy, pentalogy of Cantrell, and limb–body wall complex).[107–110] Ninety percent of FDH patients are females, and for them, the severity of the manifestations is a function of tissue mosaicism by random X chromosome inactivation in survivors. For most males, it is embryonic lethal, except for the rare cases of postzygotic somatic mosaicism. Four female patients and one 47,XXY male patient with FDH and bladder exstrophy have been found to have deleterious mutations in PORCN.[111–113] FDH is caused by inactivating mutations of the PORCN gene on chromosome Xp11.23. PORCN encodes an enzyme that governs WNT protein palmitoylation, a necessary step for WNT protein trafficking to the extracellular membrane. PORCN knockout mice demonstrate early embryonic lethality and manifest body wall anomalies, confirming that PORCN is required for gastrulation and normal embryonic development of mesoderm and ectoderm-derived structures.[114–116]

This association between FDH, PORCN, and WNT signaling is interesting because of additional findings from human exstrophy genetic studies. In 2011, Vlangos et al. performed copy number testing and candidate gene screening on 13 CE patients, but no clear causal variants were identified, except possibly two variants in the 5′ untranslated region of the WNT3 gene.[117] Studying 218 DNA samples from bladder exstrophy patients, Reutter et al. detected a genome-wide association at a highly conserved 32 kb intergenic region containing regulatory elements between WNT3 and WNT9B.[118] Using a candidate gene approach, Baranowska Korberg et al. screened 10 WNT pathway genes in 20 bladder exstrophy patients, identifying 7 novel and 13 total potentially disease-causing variants. Further screening of 410 bladder exstrophy patients for WNT3 mutations found no other significant mutations.[119] To detect changes in gene expression in bladder tissue from humans with bladder exstrophy, Qi et al. performed genome-wide expression profiling on the bladder RNAs from three normal fetuses, three normal newborns, and three exstrophy newborns, detecting altered expression of genes in (1) desmosome-mediated cell–cell adhesion, (2) cystosketal architecture, and (3) p63, PERP, SYNPO2, and Wnt pathways.[120] Mutant mouse models and mouse expression studies add credence to the body of literature that WNT signaling is crucial to mesodermal and ectodermal ventral abdominal and thoracic wall closure.[118,121,122]

Intense efforts to identify a genetic cause for human bladder exstrophy and CE have taken several approaches, including karyotyping, candidate gene screening, whole-exome sequencing, genome-wide association studies (GWASs),

and copy number variation (CNV) screening. Of 37 cases karyotyped at Johns Hopkins, two patients with exstrophy–epispadias complex had anomalies, including 47,XYY and a balanced translocation 46,XY,t(8;9)(p11.2;q13).[105] Concerning X chromosome dosage, Ramaekers et al. identified two cases of triple-X syndrome with bladder exstrophy[123] and Soderhall et al. reported a female with bladder exstrophy, short stature, and maternally inherited 46,X,der(X)(pter->P22.12::q26.3->qter).[124] One case of a microdeletion involving OTX1 on chromosome 2p15 was reported by Jorgez et al.[125] Using a variety of molecular techniques, to date, nine bladder exstrophy patients have been identified with 22q11.21 duplications[101] with delineation of a 414 kb critical region containing three screened candidate genes.[126] A candidate gene on 9q13, contactin-associated protein-like 3 (CNTNAP3), was evaluated, but a causal relationship could not be proven in bladder exstrophy.[127] After identifying a 0.9 Mb microduplication on chromosome 19p13.12 in an exstrophy patient, Draaken et al. screened the WIZ gene and found no additional mutations in 112 exstrophy patients.[128] One report of a de novo unbalanced translocation yielding monosomy from 9q34.1-qter,[129] one report of a 13 Mb deletion at 3q12.2-q13.2,[130] and two reports of a terminal deletion of chromosome 1p36.33[131,132] may indicate potential genetic loci for CE. Within the 1p36.33 locus is the DVL1 gene, encoding a phosphoprotein mediator of WNT signaling.[133] Given the multiorgan maldevelopment in CE, it is not surprising that aneuploidies such as 47,XXX,[134] 45,XO/46,XX, or 47,XX,+21 have been found.[135,136] Alx4, Gli3, Hedgehog, Ap2, Msx, p63, and PERP became candidate genes for exstrophy after knockout mice demonstrated anomalous body wall development.[101] Unfortunately, in human exstrophy, no clearly causal DNA variants have been identified in these genes after screening by GWAS, CNV testing, or gene sequencing. Reutter et al. performed whole-exome sequencing on eight CE patients and did not identify any recurrent rare variants, although they consider SLC20A1 and CELSR3 candidate genes.[101] This same collaborative group of investigators has identified ISL1 (ISL LIM homeobox 1) gene as a candidate for bladder exstrophy after their second GWAS and meta-analysis with their first GWAS.[137,138] A recent extensive CNV analysis in 169 exstrophy patients by von Lowtzow et al. found several inherited CNVs but did not identify any recurrent micordeletions or microduplications, except one in 22q11.21.[139] The role of CpG loci imprinting was investigated by DNA methylation screening in 23 exstrophy–epispadias patients, detecting hypomethylation of the PLAGL1 locus in one patient; however, its significance is unknown.[140]

Based on these findings, the exstrophy–epispadias complex is not monogenic and appears to be multifactorial with a strong genetic predisposition for susceptibility. Collaborative efforts are underway to further investigate the causes of the exstrophy–epispadias complex. If environmental factors play a role, they have not yet been identified.

Antenatal Diagnosis

Prenatal detection of bladder exstrophy or CE and male epispadias is possible by ultrasound and fetal MRI. Ultrasonography can reliably detect exstrophy before the 20th week of gestation (Figure 62.11).[80,141–148] The absence of bladder filling in the presence of normal kidneys and in association with a low-set umbilical cord suggests the diagnosis.[149] Sonographic examination may also reveal a semisolid mass protruding from the abdominal wall in association with the findings above.[150,151] Gearhart and coworkers reviewed the antenatal ultrasonographic studies of 25 women who delivered live infants with bladder exstrophy and found

- An absent bladder in 71% of the studies
- A lower abdominal protrusion in 47% of the studies
- An anteriorly displaced scrotum with a small phallus in 57% of the male fetuses
- A low-set umbilical cord in 29% of the studies
- An abnormal iliac crest widening in 18%[143]

Amniotic fluid levels are normal since urine production is normal for these fetuses. Prenatal diagnosis is valuable in the management of the exstrophies because it allows optimal perinatal management of these infants at a center equipped to treat this unusual anomaly.[93] Unfortunately, only ~25% of affected fetuses are diagnosed antenatally by ultrasound, often despite clear indicators of the diagnosis.[152,153]

Antenatal diagnosis also allows the parents the opportunity to discuss termination of the pregnancy. It is our opinion that such a discussion should include a pediatric urologist experienced in the treatment of bladder exstrophy. The overall prognosis of these children is excellent if they are treated at medical centers with physicians experienced in the treatment of this disorder. Unfortunately, because of the rarity of bladder exstrophy, healthcare providers who lack insight and knowledge of this disorder often counsel prospective parents of these patients. For example, in one recent article, the authors state, "The point of termination (of the pregnancy) may be underlined by the poor long term results in boys, who mostly end up with severe sexual dysfunction."[103] Such recommendations are based on an outdated understanding of bladder exstrophy. The present authors believe that recommending abortion for exstrophy would be akin to recommending therapeutic termination in a child diagnosed antenatally with a cleft lip or palate or ventricular septal defect. Unfortunately, the counseling of these families by healthcare providers who are unaware of the true prognosis of patients with bladder exstrophy has led to an increase in the abortion rate of these fetuses who have a treatable condition with a satisfactory long-term outcome and life expectancy when appropriately managed.[147]

Treatment Philosophies

Goals of Reconstruction of Exstrophy–Epispadias

In the treatment of exstrophy, objectives for reconstruction can be placed broadly in the following categories:

Principle objectives

- Urinary continence
- Volitional voiding
- Low-pressure urine storage
- Preservation of kidney function
- Functional and cosmetic external genitalia

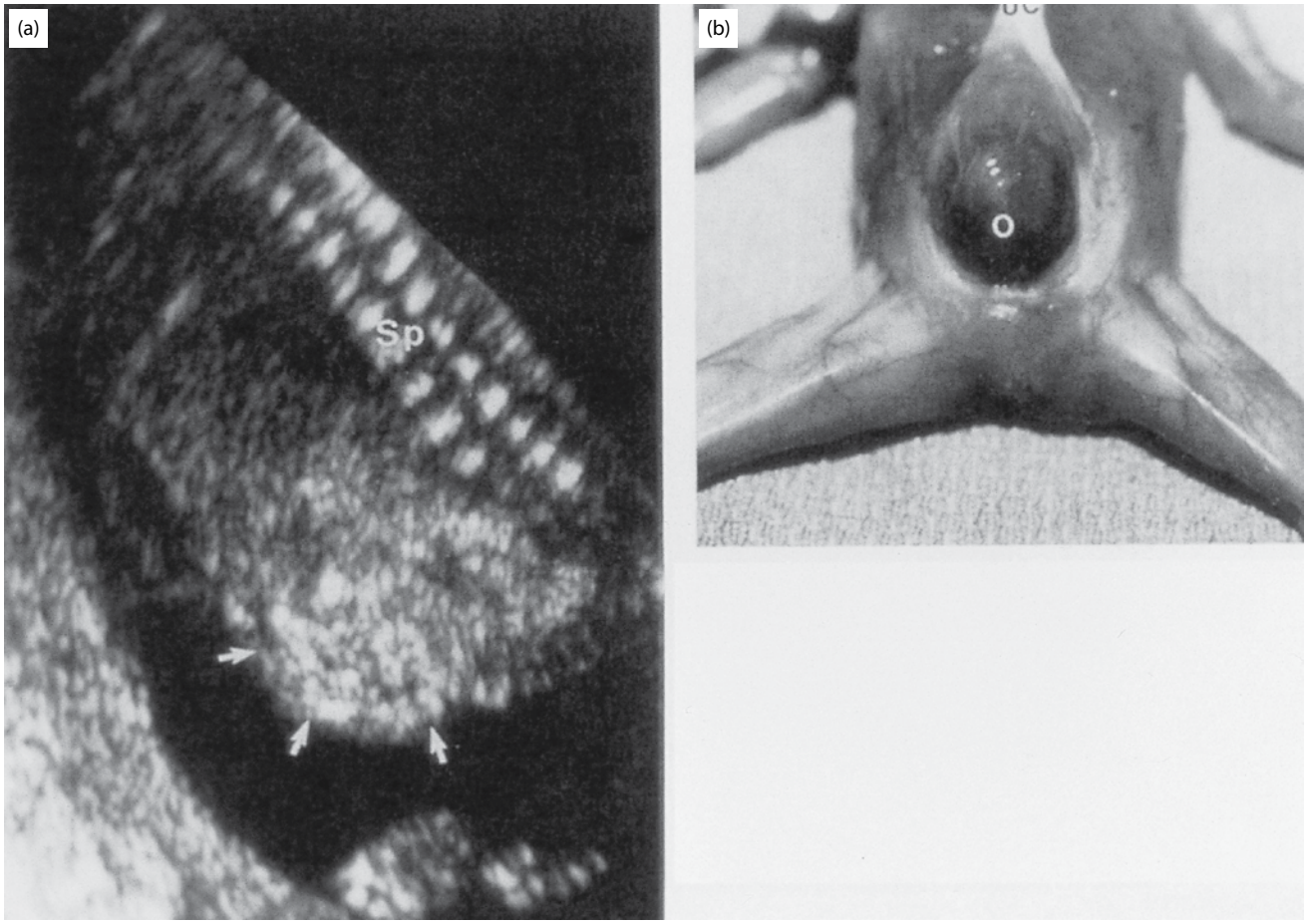

FIGURE 62.11 (a) Antenatal sonogram of a fetus with exstrophy. (b) Photograph of a fetus with confirmed exstrophy at autopsy. Sp = spine; O = omphalocele. (Adapted from Mirk P et al. *J Ultrasound Med* 1986;5(5):291–3. With permission.)

Secondary objectives

- Avoid urinary tract infections
- Reduce risk of urinary calculi
- Minimize the risk for malignancy associated with the urinary tract
- Preserve integrity of the abdominal wall fascia
- Preserve integrity of the pelvic floor

Successful achievement of these goals remains challenging. Numerous operations have been devised for the treatment of bladder exstrophy testing the ingenuity of the physicians and the resilience of the patients themselves. The objectives have expanded since the first operations were proposed and attempted in the 1800s. These objectives address the primary pathology and problems associated with exstrophy and its management. These problems include the following:

Primary pathophysiology (untreated)

- Urinary incontinence
- Urinary tract infection and renal scarring
- Urinary calculi
- Bladder malignancy
- Pelvic floor prolapse
- Inguinal herniation
- Inadequate phallus and ejaculatory dysfunction in males with subsequent sexual, social, and psychological sequelae

Potential complications (associated with management of exstrophy)

- Malignancy (related to the use of intestine in bladder reconstruction)
- Urinary tract infection
- Urinary tract obstruction
- Inadequate bladder emptying
- Urinary incontinence
- Uterine prolapse
- Severe penile shortening with dorsal chordee
- Ejaculatory dysfunction
- Urinary calculi
- Renal scarring
- Abdominal wall hernia
- Epididymo-orchitis

Natural History of Exstrophy

Bladder exstrophy–epispadias complex is not a lethal anomaly; reports exist of untreated patients with CBE living into

their eighth decade.[6] Far from debilitated, these children are often quite intelligent, with many achieving postgraduate education degrees. In contrast, until recently, patients born with CE died shortly after birth from electrolyte abnormalities and malnutrition. Because bladder exstrophy is a serious anomaly, the morbidity these patients experienced was often severe and included the problems noted above. Patients left untreated covered the exposed bladder with a variety of undergarments, including liniment-soaked rags and cotton and wool bolsters. The surrounding skin around the exstrophic bladder was often inflamed and broken down from urine contact dermatitis and secondary infection. These patients were often social pariahs because of the odor and hygiene problems. Up to the nineteenth century, many considered bladder exstrophy irreparable, as evidenced by these comments by Gross in 1876:

> Exstrophy of the bladder, unless the patient is willing to assume the (often mortal) risk of an autoplastic operation, is utterly irremediable; all that can be done is to palliate the patient's suffering by attention to cleanliness, and by the use of a closely-fitting flexible gutta-percha shield, furnished with a gum-elastic bottle for receiving urine.... When this cannot be obtained, the part must be kept constantly covered with a thick, soft compress, renewed as often as it becomes wet and disagreeable. The skin around may be protected, if necessary, with pomatum, simple cerate, or zinc treatment.[96]

Early Attempts at Surgical Reconstruction

The morbidity of exstrophy led surgeons to begin empiric approaches to the operative correction of this anomaly. Surgeons in the nineteenth century attempted urinary reconstructive or diversion procedures to treat these patients. Initial efforts were directed at partial reconstruction of the abdominal wall to allow the application of a urinary receptacle to collect urine. The first successful record of this form of repair is attributed to Dr. Pancoast in 1859. He used skin flaps from the abdominal wall:

> In the treatment of exstrophy of the bladder the principal objects aimed at are either to establish a channel for the conveyance of the urine to the rectum or perineum, or to cover its exposed and sensitive mucus membrane with flaps of skin, thereby protecting it from contact of the clothing, and preventing excoriation of the surrounding parts, as well as facilitating the adjustment of an apparatus for receiving the urine.[96]
>
> A flap is taken from one side of the abdomen or groin, dissected up, and turned over like the leaf of a book so that the epidermis comes into contact with the mucous membrane. A second flap is then taken from the groin on the opposite side and its raw surface applied to the raw surface of the former flap ... thus a thick bridge is formed over the cleft.[154]

Dr. John Wood and F. F. Maury also described variations on the use of *skin flaps* to reconstruct the abdominal wall.[96,155] Wood used a full-thickness skin graft from the abdominal wall, followed by a lateral, pyriform flap from each groin held in place with hare-lip pins, wire sutures, and broad straps of adhesive plaster that were removed

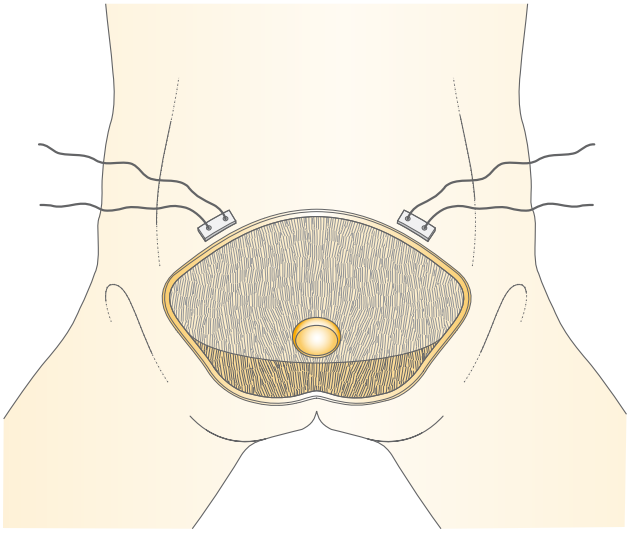

FIGURE 62.12 Early operation for bladder exstrophy, as proposed by Maury in the mid-19th century.

6–8 days after surgery (Figure 62.12). In contrast, Maury created perineal and scrotal skin flaps to repair bladder exstrophy. These procedures represented early attempts at anatomic closure but did not address the functional reconstruction of these bladders—namely, to achieve satisfactory storage and emptying of urine. V. H. Van Buren aptly stated the common sentiment of the time:

> The most that can be promised by operative interference is to leave behind a fistula, more or less large, over which a urinal must be constantly worn. The patient's virility is not returned to him, nor is his condition very materially bettered. A less dangerous and equally efficacious mode of treatment seems to be to adapt a suitable urinal to the parts as they are left by Nature, such a one as shall shield them from injury, and keep the patient dry and clean.[156]

Others, such as Simon, approached the surgical treatment by attempting *urinary diversion* in these patients through the creation of a ureteral sigmoid fistula. Results were poor; one patient died of peritonitis in the immediate postoperative period, and the other died of renal failure secondary to chronic pyelonephritis.[96]

These early efforts suffered from lack of understanding of the physiology of the urinary tract and bladder, and subsequently how these operations would affect urine storage and emptying, kidney function, electrolyte homeostasis, the propensity for urinary tract infection or calculus formation, fertility, and sexual function. Complications from these operations, as noted above, were often life threatening. The fact that patients were willing to assume the risk of surgical death demonstrates the impact this anomaly had on their lives.

Modern Era: Operative Procedures in the Management of Exstrophy

A host of operations for exstrophy have been proposed and attempted, which may be broadly characterized into two

approaches: (1) removal of the exstrophic bladder with replacement by a urinary diversion or (2) anatomic functional exstrophic bladder reconstruction either in multiple stages or in a single stage. Surgeon preference, patient anatomy, previous surgical procedures, availability of tertiary care facilities, and access to medical care all play a role in which operative procedure is chosen for a particular patient. Even in the twenty-first century, no standard of care exists for this patient population. However, because of the complexity of care involved and the rarity of this congenital defect, centers of excellence and specialists with an interest in the exstrophy–epispadias complex usually manage these patients most effectively.[88,89,93] Recently, a U.S. multi-institutional collaborative consortium has formed to maximize individual and collective surgeon experience and knowledge while standardizing management and surgical technique, with the ultimate goal of improving short- and long-term outcomes for these challenging surgical patients.[157]

Perioperative Care of the Patient with Exstrophy

Preoperative Care

With rapid referrals and, in some cases, prenatal diagnoses, neonates with bladder exstrophy should be evaluated for surgical reconstruction promptly. To prevent trauma to the exposed bladder plate after delivery, the umbilical cord should be ligated with silk suture rather than a plastic or metal clamp. An ideal protective covering for the exstrophic bladder is a hydrated gel dressing such as Vigilon®, if available. If a hydrated dressing is unavailable, covering the exposed bladder with plastic wrap (Saran Wrap®), especially for transportation, is an acceptable alternative. These protect the bladder plate effectively and allow handling of the infant with minimal risk of trauma to the bladder. In some circumstances, Vigilon has been used for more than 2 months with minimal inflammation of the bladder noted at the time of repair. The dressing should be replaced daily and the bladder irrigated with normal saline with each diaper change. Others advocate the use of a humidified air incubator with no dressing at all to minimize bladder trauma.[43] Often, the keratinized skin around the bladder plate becomes inflamed from the chronic urine exposure; barrier creams (zinc oxide) help prevent this.

Some exstrophic bladders are extremely small, acontractile, and nondistensibile.[158] Although bladder cycling is known to stimulate bladder growth, in some cases, an early attempt at closure will only result in upper tract deterioration. Although this is a subjective decision, delay of closure may give more time for bladder plate growth. Two reports have also indicated that exstrophy closure in the premature infant should be discouraged due to higher complication rates.[159,160]

Routine use of intravenous antibiotic therapy in the pre- and postoperative period decreases the chance for bacterial infection; however, candidal infection may supercede. A baseline sonogram should be obtained to assess the kidneys preoperatively for later comparisons. A preoperative kidney, ureter, and bladder (KUB) can delineate the extent of pubic symphysis diastasis. A spinal sonographic examination should also be obtained if sacral dimpling or other signs of spina bifida occulta are noted on physical examination in the child under the age of 6 months. After this age, MRI will be necessary to image the spinal cord. Orthopedic consultation is advisable to plan osteotomies if needed, and neurosurgical consultation is required for children with spinal anomalies.

Operative Considerations

Most children with epispadias and bladder exstrophy have no additional anesthetic risk factors, but CE patients often have comorbidities. CE patients with short gut will likely require long-term central venous access at the time of surgery. Exstrophy closure is performed using general inhalation anesthesia, avoiding nitrous oxide to minimize bowel and peritoneal distension and maximize surgical exposure. The use of a nasogastric tube to minimize abdominal distention is controversial.[14,161] Regional anesthesia can be achieved by a one-time caudal block to reduce the inhaled anaesthetic requirement during the operation or in the older child, via a continuous-infusion epidural.

General Comments on Osteotomies

Trendelenberg first recognized the importance of osteotomies in exstrophy closure at the turn of the century. Osteotomies optimize pubic symphysis apposition, diminish tension on the closure, and optimize anatomic placement of the bladder, bladder neck, and urethra in the pelvis. They also improve the reapproximation of the corporal and clitoral bodies. Finally, osteotomies may decrease the chance for later uterine prolapse because the anterior closure brings the pelvic diaphragm into a more normal anatomic position to offer more support.

The need for osteotomy is best determined under general anesthesia. Candidates for osteotomy include those more than 72 hours old, newborns with a wide pubic diastasis of >4 cm, newborns with CE, those with a nonmalleable pelvis not permitting pubic apposition, and patients who have had a previously failed closure.[162] Osteotomies are usually performed at the same setting as bladder closure to help secure the closure.

Osteotomies may be performed by an anterior or posterior approach or a combination of approaches.[163] Posterior iliac osteotomies are performed with the patient in a prone position, after which the patient is then repositioned for the bladder closure. However, increased blood loss and occasional malunion of the ileum have caused this approach to fall out of favor. Anterior iliac osteotomies offer the advantage of a single position and sterile field preparation (Figures 62.37 and 62.38). Anterior diagonal iliac osteotomies have been preferred by the Seattle group. Compared with posterior iliac osteotomies, an anterior approach has also been shown to result in less blood loss and better apposition and mobility of the pubic rami. The group at Johns Hopkins has advocated for bilateral combined anterior innominate and vertical iliac osteotomies (Figure 62.13) because of their experience of superior initial and long-term results compared with anterior iliac osteotomies alone.[32,164] Both osteotomies may be performed through the same anterior skin incision on each side and with minimal blood loss and a 4% complication rate (Figure 62.14).[164,165] McKenna has also described the use of a diagonal midiliac osteotomy performed through

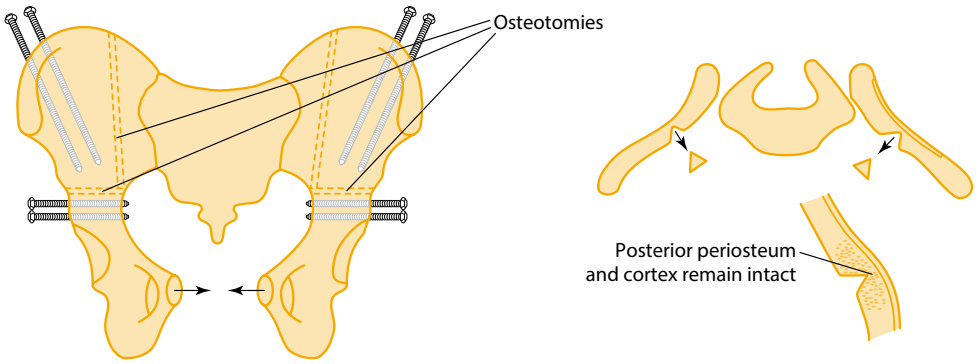

FIGURE 62.13 Osteotomy sites for combined vertical iliac and transverse innominate osteotomies showing the placement of intrafragmentary pins.[103]

the same incision as the exstrophy closure.[166] Division of the superior pubic ramus has also been described; it is not as effective as the other methods described but may be used in the newborn period.[167,168] In older children, a bone graft may be used to stabilize the osteotomy.[166]

Postoperative Considerations

Several methods have been used to maintain pelvic ring closure and prevent external hip rotation following bladder closure without osteotomies. Mummy wrapping can be unreliable, and some believe it should not be used.[14] High-volume exstrophy centers debate over the best method. The two most commonly employed in the newborn period are modified Bryant's traction for 4 weeks[1] (Figure 62.15) and spica casting for 3–6 weeks (Figure 62.16).[169] If osteotomies are performed, they are secured with interfragmentary pins and external fixation with light Buck's traction for 2–4 weeks (Figure 62.17). Some fit the newborn with a "sled" to be used when the child is out of traction for feeding and bathing in these situations. Traction does make performing daily activities and routine care difficult, but spica casting can permit more mobility of the infant pelvis.

Low-dose antibiotic prophylaxis is commonly prescribed, since vesicoureteral reflux is nearly universal. This is continued until vesicoureteral reflux is corrected or resolves spontaneously.

Postoperative factors recognized to increase the success of the initial reconstruction[170] include

- Use of osteotomies (in selected cases) or newborn closure (<24–48 hours)
- Postoperative immobilization
- Use of postoperative antibiotics
- Ureteral stenting catheters
- Adequate postoperative pain management
- Avoidance of abdominal distension
- Adequate nutritional support
- Secure fixation of urinary drainage catheters

Exstrophy Closure: Anatomic Reconstruction

The first efforts at anatomic reconstruction of the exstrophic bladder are usually attributed to Trendelenberg.[171] In 1881, he described an exstrophy closure emphasizing the importance of pubic reapproximation in front of the reconstructed bladder to achieve continence and prevent dehiscence. This effort ultimately proved unsuccessful. Because of discouraging results such as this, bladder reconstruction in exstrophy was largely abandoned and

FIGURE 62.14 Single postoperative incision for combined vertical iliac and transverse innominate osteotomies with interfragmentary pins. (Photo courtesy of John Gearhart MD.)

FIGURE 62.15 Patient seen in Bryant's traction after exstrophy closure without osteotomies. (Photo courtesy of John Gearhart MD.)

FIGURE 62.16 Use of a spica cast following complete primary repair for exstrophy to reduce tension on the closure by preventing hip abduction in the postoperative period.

FIGURE 62.17 Patient seen with an external fixator and in modified Buck's traction. (Photo courtesy of John Gearhart.)

replaced by urinary diversion, most notably ureterosigmoidostomy, in the early part of this century.

Not all attempts at bladder reconstruction for exstrophy were abandoned. Various surgeons reported occasional successful attempts at bladder reconstruction during this time. However, these results were uncommon and difficult to reproduce. For example, H. H. Young reported the first successful primary bladder closure in 1942. He achieved urinary continence after reconstruction in a young girl.[172] Primary reconstructive efforts by others remained inconsistent and largely unsuccessful during this period. Since Young's successful report in 1942, other investigators have intermittently achieved a satisfactory result with a one-stage reconstructive effort to repair the exstrophied bladder. Ansell reported on a one-stage closure in 1971 with a successful outcome in a newborn female.[173] Ansell was also one of the early advocates for primary closure of bladder exstrophy in the newborn period and reported 28 cases closed in this fashion.[174] Montagnani described a one-stage functional bladder reconstruction in two female babies aged 8 and 13 months. His bladder reconstruction procedure included inominate osteotomy, bladder closure, an antireflux procedure, and narrowing of the bladder outlet, followed by pubic reapproximation. Continence was achieved in one of the two patients. The second patient required further bladder neck reconstruction (BNR) to achieve continence.[175] Fuchs also achieved urinary continence in 8 of 15 patients who were also repaired in a single-stage effort.[176] However, several large series of patients who underwent single-stage reconstruction in the 1960s and 1970s reported continence rates of only 10%–30%.[177–182] Renal damage was as high as 90% in these series, generally because of bladder outlet obstruction.[178]

Because of these complications and the low rate of urinary continence, reconstructive surgical efforts were subsequently directed toward planned staged bladder reconstruction. Staged reconstruction with osteotomies was pioneered and advocated by Jeffs, Chisholm, and Ansell in the 1970s and further refined by Gearhart and others as the modern staged repair of exstrophy (MSRE).[36,174,183,184] An alternative staged reconstruction without osteotomies, the radical soft tissue mobilization (RSTM) technique, was reported by Kelly.[185] Recent advances in single-stage reconstruction for neonatal and older exstrophy have been advocated by Fuchs[176] and others; as such, the complete primary repair for exstrophy (CPRE) by Mitchell has gained favor.[186]

All approaches aim to reconstruct and achieve anatomic and functional normalcy with minimal surgical morbidity. In the subsequent section, the three currently favored surgical techniques, CPRE, RSTM, and MSRE, are detailed. In reality, closure of the female with bladder exstrophy is not significantly different in these methods; the end result is closure of the bladder, urethra, and abdominal wall. In contrast, closure of the male with bladder exstrophy is quite different in CPRE, RSTM, and MSRE. CPRE closes and repositions the bladder and entire urethra at one stage. In contrast, MSRE and RSTM close and reposition the bladder and posterior urethra at the first stage, with the remainder of the urethra closed at a later stage. CPRE and RSTM both completely disassemble the penis into its three components, while MSRE maintains urethral attachment to the glans.

Complete Primary Repair for Exstrophy

In the late 1980s, an anatomic approach to exstrophy repair that combined simultaneous bladder closure, bladder neck remodeling, and epispadias repair was initiated by Mitchell.[186] This operation evolved out of a technique developed for the treatment of epispadias—the complete penile disassembly technique.[187]

Complete primary reconstruction of the exstrophied bladder is best done in the newborn period. Primary reconstruction in the newborn period is technically easier than when done in an older child. It also offers theoretical advantages, as it may maximize the opportunity for "normal" bladder development and the potential for urinary continence. The bony pelvis remains pliable in the newborn period, so that osteotomies may be avoided in some cases—usually if closure can be performed within the first 72 hours of life.

Clinical experience with patients with posterior urethral valves suggests that early restoration of nonobstructive emptying and filling of the bladder allows the bladder to regain some or all of its normal physiologic and

developmental potential.[188] This, in turn, implies that the bladder progresses through developmental milestones that occur in the first few months of life and which may be irreversibly lost if missed. Precedence for this form of organ development is noted in the brain with the acquisition of language and visual perception. Finally, early primary bladder reconstruction creates a more normal-appearing baby that fosters improved bonding between the parents and infant.

In the complete primary repair or Mitchell technique,[186] the bladder, bladder neck, and urethra are moved posteriorly within the pelvis. This movement positions the proximal urethra within the pelvic diaphragm in an anatomically more normal position to maximize the effect of the pelvic muscles and support structures in the achievement of urinary continence. Posterior movement of the bladder neck and urethra also facilitates reapproximation of the pubic symphysis that in turn helps prevent anterior migration of the urethra and bladder neck and provides a more anatomically normal muscular pelvic diaphragm.

Total penile disassembly reduces anterior tension on the urethra because it is separated from its attachments to the underlying corporal bodies. These attachments otherwise pull the urethral plate anteriorly, preventing posterior placement of the proximal urethra and bladder neck in the pelvis. Tension reduction theoretically decreases the risk of bladder dehiscence and also temporarily reduces the dorsal tension on the corporal bodies that may contribute to dorsal chordee in males. Combining the epispadias repair with primary closure allows for the most important aspect of primary closure—division of the intersymphyseal ligament or band located posterior to the urethra in these patients. Advocates of CPRE feel that division of this ligament and deep dissection is optimized when the urethra is separated from the corpora cavernosa.

Neonatal closure employing this technique optimizes the chance for early bladder cycling and consequent normal bladder development. It may also obviate the need for a multistaged repair of the exstrophied bladder, including further BNR, bladder augmentation, and penile reconstructive surgery. This is not uniform however, as the Boston group found BNR needed in up to 40% of CPRE closures.[189]

Male CPRE Technique

The surgical technique of CPRE and the Mitchell complete penile disassembly technique for epispadias follow the same principles and thus are discussed simultaneously. After standard preparation of the surgical field, 3.5 French umbilical artery catheters are placed into both ureters and secured with a 5.0 chromic suture. A marking pen outlines the planned lines of dissection (Figures 62.18 and 62.19). Initial dissection begins superiorly and proceeds inferiorly to separate the bladder plate from the adjacent skin and fascia using fine-tip electrocautery (Colorado® tip). The umbilical cord usually needs to be mobilized on its vessels in a cephalad direction such that the resulting umbilicus will be at the level of a line drawn between the two iliac crests. The relocated umbilicus will also be the cutaneous site for bringing out the suprapubic tube. The dissection in classic exstrophy patients is extraperitoneally.

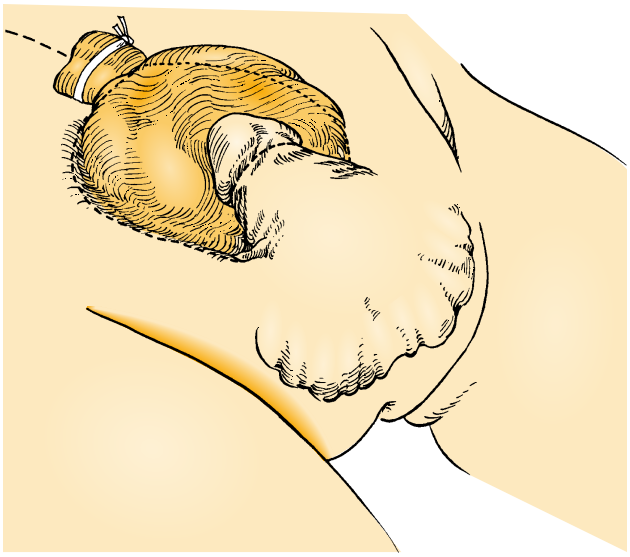

FIGURE 62.18 Initial lines of dissection for male complete primary exstrophy repair technique – ventral perspective.

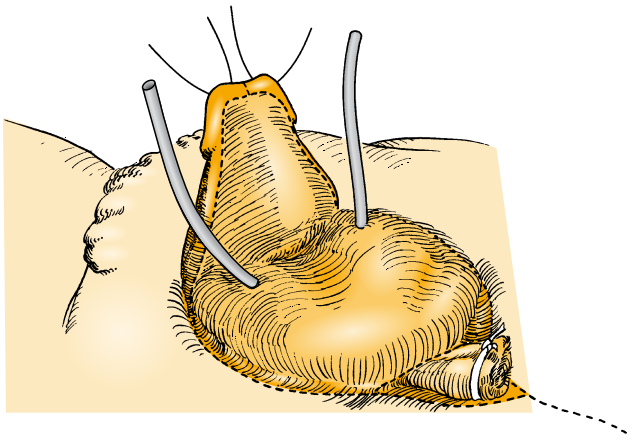

FIGURE 62.19 Initial lines of dissection for male complete primary exstrophy repair – dorsal perspective. Lines at the bladder neck indicate approximate tailoring that may be needed to exclude dysplastic tissue in this area.

To aid in dissection, traction sutures are placed into each hemiglans of the penis. These sutures are placed at the beginning of the operation and are initially oriented *transversely* in the hemiglans. The sutures will rotate to a parallel vertical orientation as the corporal bodies rotate medially following dissection of the corporal bodies and the urethral wedge (urethral plate plus underlying corpora spongiosa) from each other.

To begin the penile dissection, a circumcising incision is made along the ventral aspect of the penis. This should precede dissection of the urethral wedge from the corporal bodies because it is easier to identify Buck's fascia ventrally. The initial plane of dissection is developed just above Buck's fascia. *Buck's fascia stops at the corpora spongiosum during the dissection.* So, as the dissection progresses medially, the plane shifts subtly from above Buck's fascia to just above the tunica albuginea. Dorsally,

methylene blue or brilliant green helps differentiate urothelium from squamous epithelium. Injection of the surrounding tissues with 0.25% lidocaine and 1:200,000 μ/mL epinephrine also improves hemostasis, which assists the dissection. The margins of the dorsal urethra are usually obvious. The surgeon must take care not to narrow the urethral wedge, as this will be tubularized later. Urethral wedge dissection is carried proximally to the bladder neck. Careful lateral dissection of the penile shaft skin and dartos fascia from the corporal bodies is paramount; the lateral dissection of the penis is always superficial to Buck's fascia because the neurovascular bundles are located laterally in the epispadic penis. Medially, under the urethral wedge, the dissection plane is on the tunica albuginea of the corpora cavernosa.

The penis is surgically disassembled into three components—the right and left corporal bodies with their respective hemiglans and the urethral wedge (urothelium with underlying corpora spongiosa).[187] *This is done primarily to provide exposure to the intersymphyseal band and to allow adequate proximal dissection*. It is easiest to initiate the dissection proximally and ventrally (on the underside of the corpora cavernosa) (Figure 62.20). The plane of dissection should be carried out at the level of the tunica albuginea on the corpora. After a plane is established between the urethral wedge and the corporal bodies, this dissection is carried distally to separate the three components from each other (Figure 62.21). This maximizes the degree of freedom for the best repair. The corporal bodies may be completely separated from each other since they exist on a separate blood supply. It is important to keep the underlying corpora spongiosa with the urethral plate; the blood supply to the urethral plate is based on this corporal tissue, which should appear wedge shaped after its dissection from the adjacent corpora cavernosa. The urethral or corporal spongiosal component will later be tubularized and placed ventral to the corporal bodies. Paraexstrophy skin flaps should not be used for urethral lengthening because this maneuver may devascularize the distal urethra. Because the bladder and urethra are moved posteriorly into the pelvis as a unit, division of the urethral wedge should *never* be necessary. However, in some cases, a male patient will be left with a hypospadias that will require later surgical reconstruction (short distal urethra).

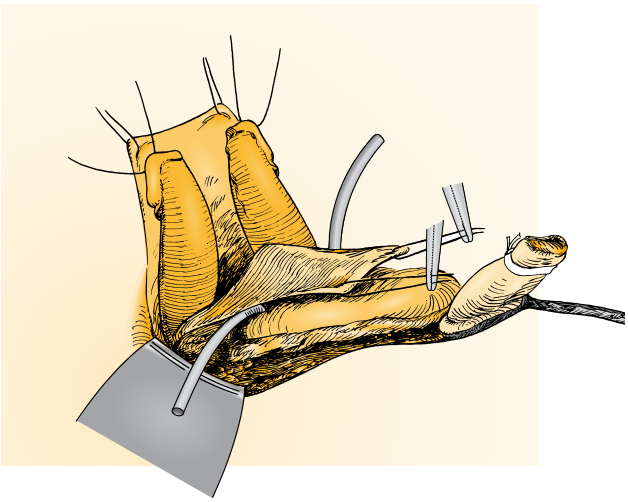

FIGURE 62.21 Distal separation of the corporeal bodies and urethral wedge. This maneuver may not always be required. Complete separation allows maximal exposure to the pelvis and optimizes the dissection and posterior positioning of the bladder, bladder neck, and urethra in the pelvis.

Proximal dissection of the urethral wedge from the corporal cavernosa bodies facilitates exposure of the intersymphyseal ligament, which must be incised. The dissection may be carried into the pelvis following the planes along the medial aspects of the corporal bodies (Figure 62.22). *Deep incision of the intersymphyseal ligaments posterior and lateral to each side of the urethral wedge* is absolutely

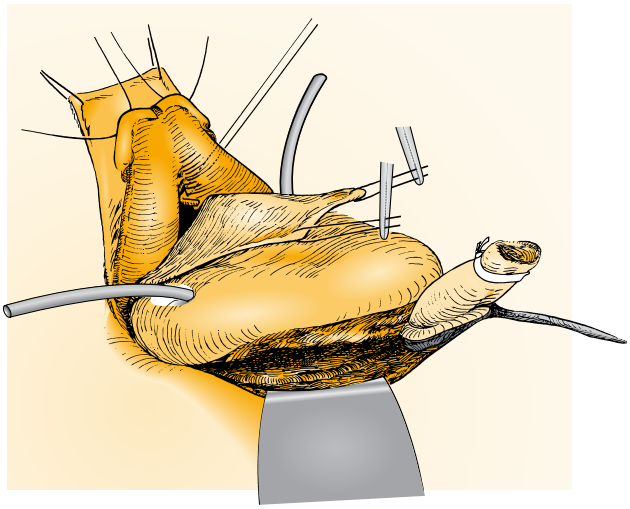

FIGURE 62.20 Disassembly of the urethral wedge (urethral plate with underlying corpora spongiosa) from corporeal bodies. The plane of dissection should remain on the corporeal bodies to allow the corpora spongiosa to remain with the urethra.

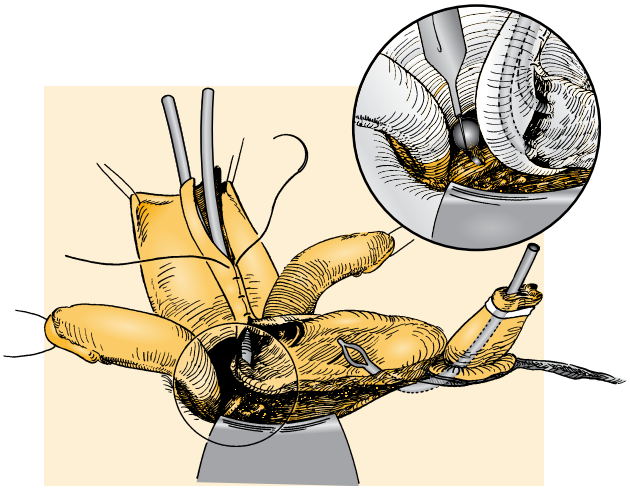

FIGURE 62.22 Division of the intersymphyseal band (condensation of anterior pelvic fascia) and deep pelvic dissection. The inset demonstrates division of the intersymphyseal band. Division of this band allows posterior placement of the bladder without tension.

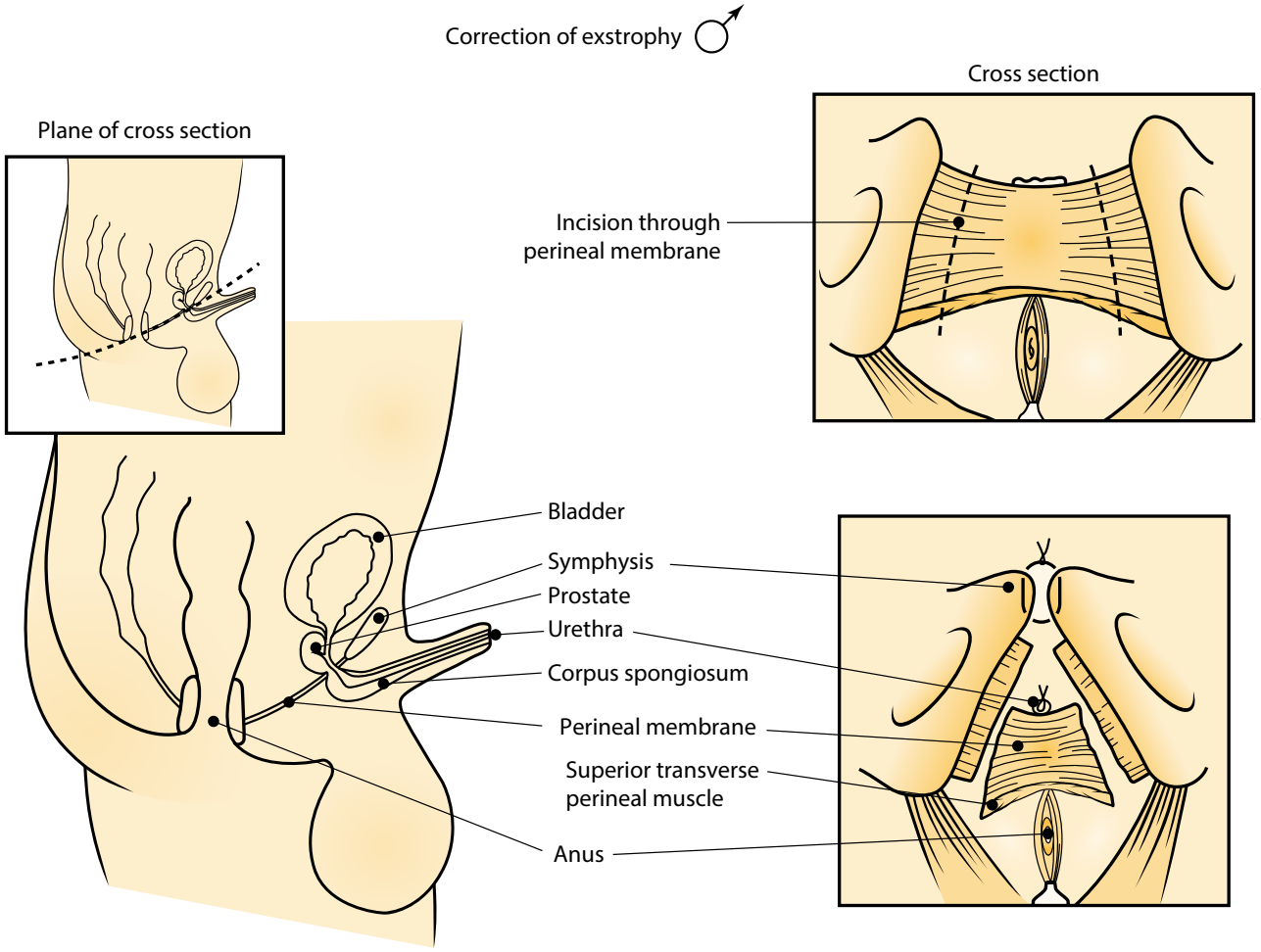

FIGURE 62.23 This cross section represents an idealized positioning of the urethra and bladder neck in the pelvis.

necessary to allow the bladder to achieve a posterior position in the pelvis (Figure 62.23). This dissection should be carried until the pelvic floor musculature becomes visible (i.e., the intersymphyseal ligament is completely incised). Computerized tomography of the pelvis demonstrates that these ligaments lie posterior to the bladder neck and urethra. Failure to adequately dissect the bladder and urethral wedge from surrounding structures will create anterior tension along the urethral plate and prevent posterior movement of the bladder in the pelvis.

Once the bladder and urethral wedge are adequately dissected from the surrounding tissues, the majority of the procedure is done and the closure is straightforward and anatomic. The importance of recognizing the proper location of the bladder neck is key (in boys proximal to the verumontanum and in girls just distal to the trigone). Prior to reapproximating the bladder, a suprapubic tube is placed and brought out through the umbilicus. The primary closure of the bladder is achieved using a three-layer closure with monofilament absorbable suture (i.e., Monocryl® and Vicryl®). The urethra is tubularized using a two-layer running closure with monofilament and Vicryl suture as well (Figure 62.24). The tubularized urethra is then placed ventral to the corpora in an anatomically normal position.

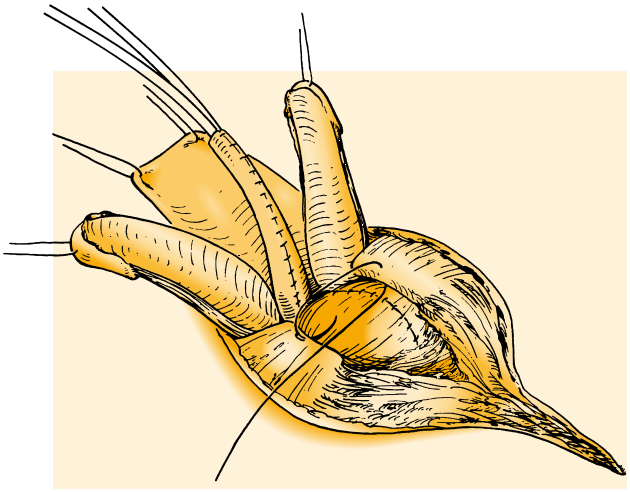

FIGURE 62.24 The bladder and urethra are closed in two layers using absorbable suture. The ureteral catheters are brought out throught the urethral closure. The suprapubic tube may be brought out through the umbilicus.

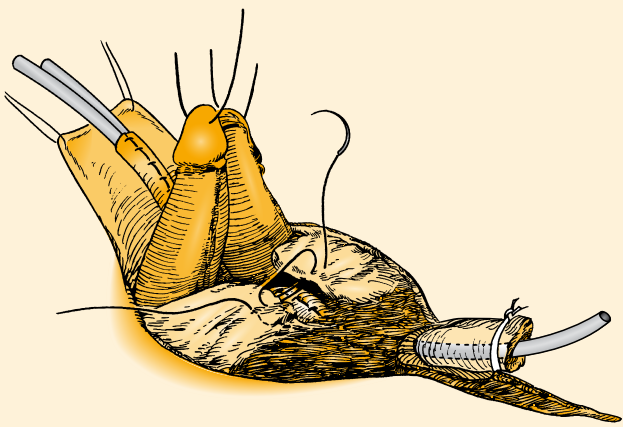

FIGURE 62.25 Reapproximation of pubis symphysis using absorbable suture. Note medial rotation of glans that occurs after dissection.

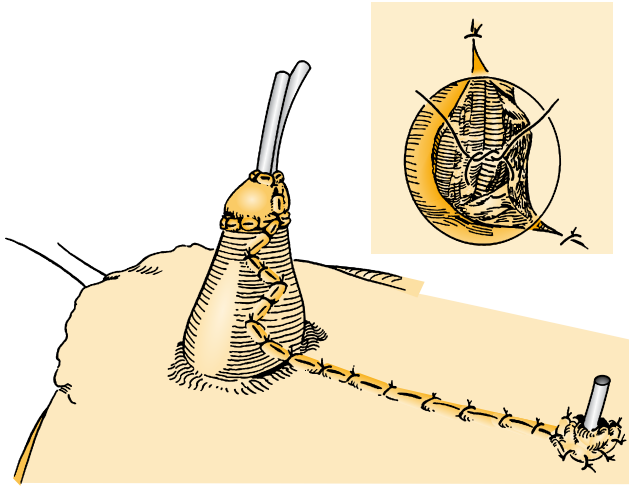

FIGURE 62.26 Skin reapproximation can be challenging. Tacking sutures placed between the dermal tissue and the corporeal bodies can assist in anchoring the penile shaft skin to the base of the penis. Z-plasty incisions can also be useful to approximate the shaft skin ventrally.

Then the pubic symphysis is reapproximated using a 0.0 polydiaxonone-interrupted figure of eight sutures. Knots are anterior to prevent suture erosion into the bladder neck (Figure 62.25). Rectus fascia is reapproximated using a running 2.0 polydiaxonone suture. Penile shaft skin is reconfigured using either a primary dorsal closure or reversed Byars flaps, if needed, to provide dorsal skin coverage. Skin covering the abdominal wall is reapproximated using a two-layer running closure of absorbable monofilament suture.

The corporal bodies will tend to rotate medially with closure when the lateral margins of Buck's fascia of each corpora cavernosa are approximated. This rotation will assist in correcting the dorsal deflection and can be readily appreciated by observing the vertical lie of the previously horizontally placed glans traction sutures. Occasionally, significant discrepancies in the dorsal and ventral lengths of the corpora will require dermal graft insertion. However, this is rarely needed in the newborn closure. The corpora are reapproximated with fine interrupted suture along their dorsal aspect.

The urethra can then be brought up to each hemiglans ventrally to create an orthotopic meatus (Figure 62.26). The glans is reconfigured using interrupted mattress sutures of polydiaxonone suture (i.e., PDS®), followed by horizontal mattress sutures of 7.0 monofilament suture (i.e., Maxxon®) to reapproximate the glans epithelium. The neourethra is matured with 7.0 braided polyglactin suture (i.e., Vicryl) similar to a standard hypospadias repair. In some, the glans tissue is reduced to create a conical-appearing glans. In roughly half of cases, the urethra lacks enough length to reach the glans. In this situation, the urethra may be matured along the ventral aspect of the penis to create a hypospadias (Figure 62.27). This can be corrected at a later date as a second-stage procedure, and options for hypospadias repair are detailed in other chapters. The redundant shaft skin is maintained ventrally in these patients to assist in later penile reconstructive procedures.

Female CPRE Technique

The principles and timing of repair are analogous for boys and girls (Figure 62.28a and b). To perform this technique, the lines of initial dissection are depicted in Figure 62.29. *In an effort to clearly define the bladder neck, the bladder neck dissection is tailored*. The bladder neck, urethra, and vagina are mobilized as a unit. The dissection is achieved with a tungsten-tip electrocautery (Colorado tip) to minimize tissue damage while achieving hemostasis. The appropriate plane of dissection is found anteriorly along the medial aspect of the bifid clitoris and proceeds posteriorly along the lateral aspect of the vaginal vault (Figure 62.30). *The vagina is mobilized with the urethral plate and bladder neck. The urethra and bladder neck should not be dissected from the anterior vaginal wall*, as this will compromise the blood supply to the urethra.

During the posterior lateral dissection, the intersymphyseal band will be encountered and should be deeply incised to allow the vagina, urethra, and bladder neck to move posteriorly. The posterior limit of the dissection is

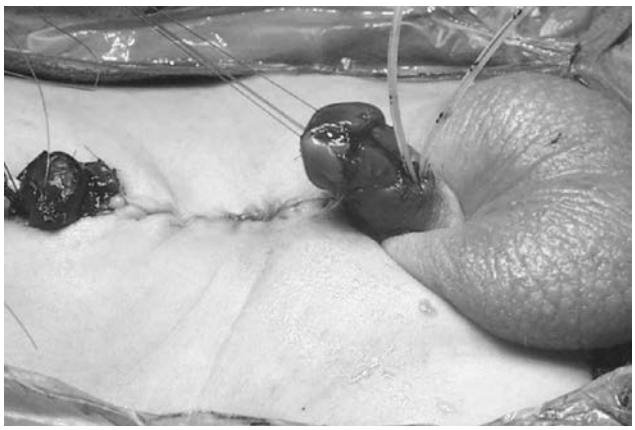

FIGURE 62.27 Hypospadias occurs in this situation because the urethra is too short after the bladder has been positioned posteriorly in the pelvis.

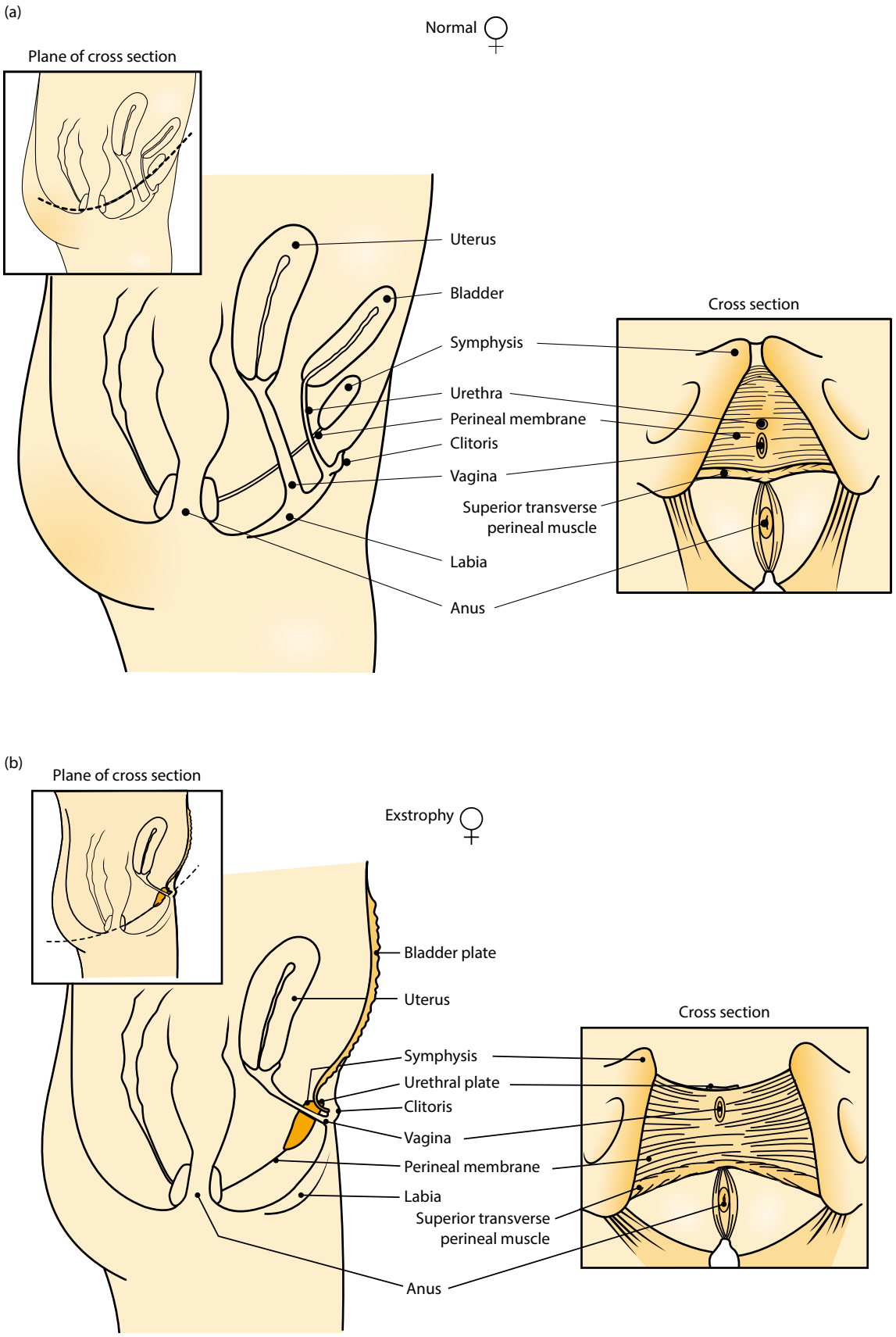

FIGURE 62.28 Cross section of (a) normal female anatomy compared with (b) exstrophic female anatomy.

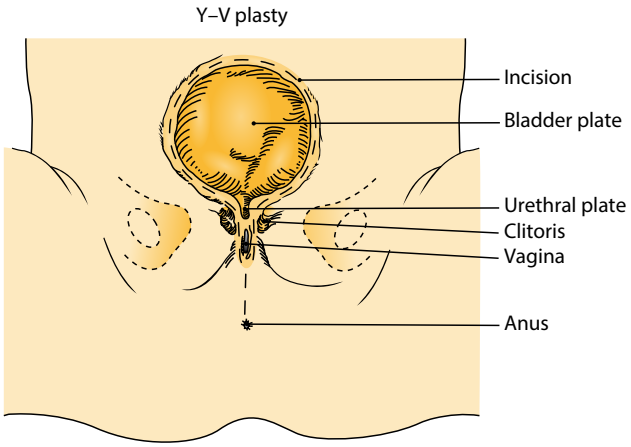

FIGURE 62.29 Initial lines of dissection for female complete primary exstrophy repair technique. Of note, the dissection is carried around the vaginal vault inferiorly to mobilize the vagina and urethra together.

reached when the pelvic floor musculature is exposed. The proximal urethra can be lengthened to some degree with parallel incisions in the bladder plate toward the trigone. As importantly, lateral dysplastic tissue should be removed from the region around the bladder neck when the bladder neck is created.

Following adequate dissection, the vagina and urethra are moved posteriorly in the perineum with a Y-V plasty. The urethra is then tubularized using a two-layer closure of absorbable suture (Figure 62.31). Prior to the urethral closure, a suprapubic tube is routinely placed to provide postoperative urine drainage (Figure 62.32). The bladder, bladder neck, and urethra should be positioned deeply in the pelvis and traverse the pelvic diaphragm (Figure 62.33). The pubis symphysis is then reapproximated using two 0.0 PDS figure eight sutures (Figure 62.34).

As in the repair in the boy, *osteotomies may be necessary* when a wide pubic diastasis prevents a low-tension reapproximation of the pubic symphysis. Mitchell and Grady use anterior iliac osteotomies in these situations.

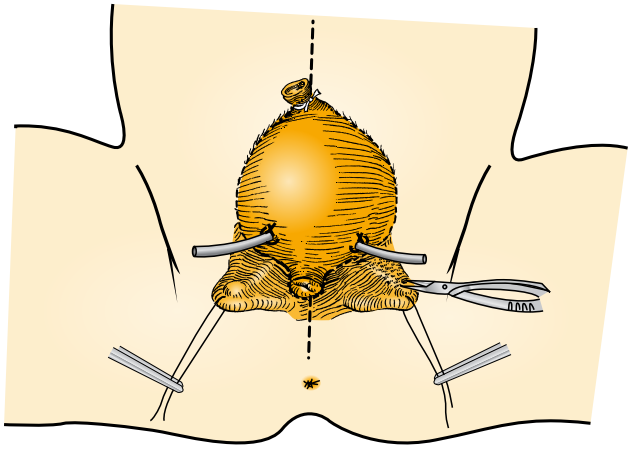

FIGURE 62.30 The lines of dissection are marked in this drawing of a newborn girl with classic bladder exstrophy. Please note stay sutures placed in clitoral bodies to assist with exposure.

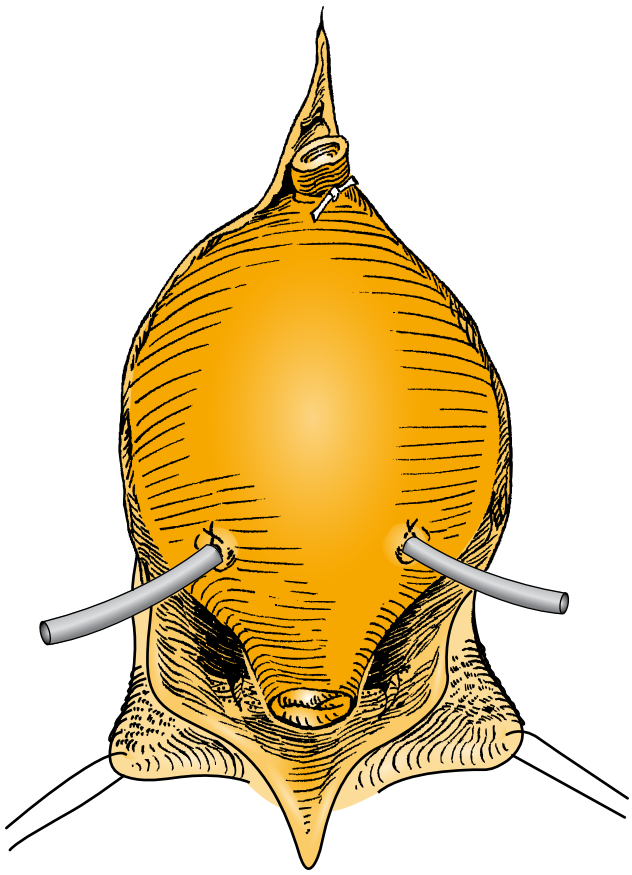

FIGURE 62.31 The appropriate plane of dissection is found anteriorly along the medial aspect of the bifid clitoris and proceeds posteriorly along the lateral aspect of the vaginal vault. This allows for deep pelvic dissection to place the bladder, bladder neck, and urethra into the pelvis without tension.

The rectus fascia can then be closed in the midline. The neourethra is matured with 5.0 Vicryl sutures and reapproximates the already denuded bifid clitoris medially so that they fuse together after suturing with 7.0 Maxxon suture. The labia majora is advanced posteriorly to the perineum at this time to improve cosmesis of the external genitalia (Figure 62.35). A Z-plasty skin closure can be employed as well.

Modifications of the CPRE Technique

In an effort to improve the results of the CPRE technique, several authors have reported modifications. Caione and colleagues described the use of an electrical muscle stimulator during deep pelvic dissection to preserve and reconfigure the periurethral muscle complex. Long-term results of this patient series have not yet been reported; preliminary results are promising.[190]

El-Sherbiny and Hafez have described a modification of the penile disassembly technique preserving the connection between the distal urethral wedge and the corporal bodies to decrease the incidence of hypospadias.[191] Proposed by Emir and colleagues, one solution for intraoperatively anticipated hypospadias is to generate parameatal-based inner preputial skin flaps that do not require anastomosis to the urethral plate.[192]

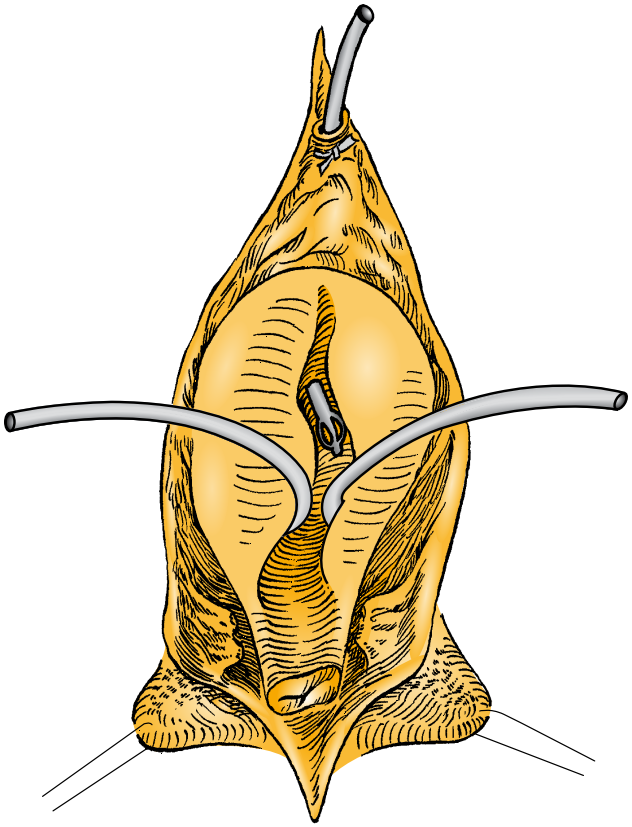

FIGURE 62.32 Prior to the urethral closure, we routinely place a suprapubic tube to provide postoperative urine drainage. The suprapubic tube is brought out through the umbilicus. Ureteral catheters are left in place and brought out through the urethra. All tubes are left to gravity drainage.

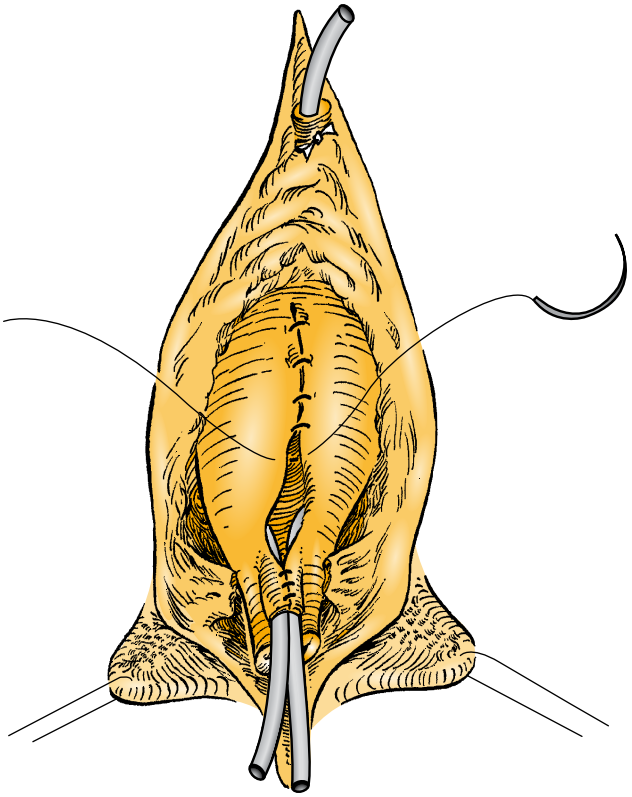

FIGURE 62.33 The bladder, bladder neck, and urethra should be positioned deeply in the pelvis if an adequate dissection has been performed.

Other primary modifications include the technique pioneered by Dr. Kureel. By employing a novel midline scrotoperineal approach, he has been able to more readily identify the nerves in the perineal region to facilitate an innervation preserving sphincteroplasty and radical corporal detachment for reconstruction of exstrophy–epispadias.[193,194]

Outcomes of CPRE

The longest series reporting outcomes of CPRE is from Seattle Children's Hospital, spanning 20 years. Of 39 patients, the median follow-up is 106 months for the original group reported in 1999 and 58 months for the entire series. Of the children older than 4 years of age, 74% have gained daytime continence with volitional voiding. Of these children, 20% of boys and 43% of girls have achieved incontinence without the need for BNR or tailoring. In the remainder, bladder neck modification was performed prior to achieving continence. The majority of these bladder neck modifications were performed at the same time as ureteral reimplantation procedures and were performed using a Mitchell bladder neck technique. An 18% complication rate has been noted in this series.[195] One other report from the Boston group provides an 8-year follow-up of CPRE outcomes. Borer and colleagues noted that 5 of 8 patients (63%) 4 years old

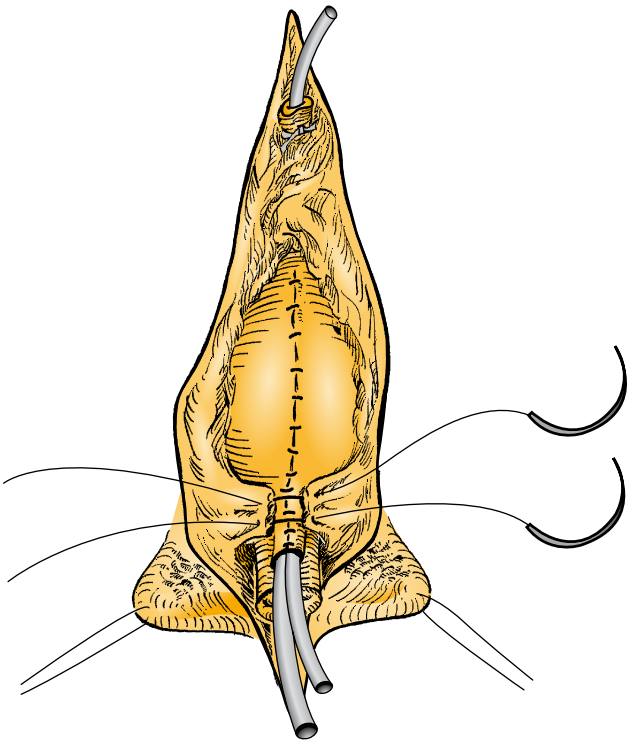

FIGURE 62.34 Reapproximation of symphysis pubis using interrupted sutures. Lateral dissection may be required to reapproximate the rectus fascia in the midline.

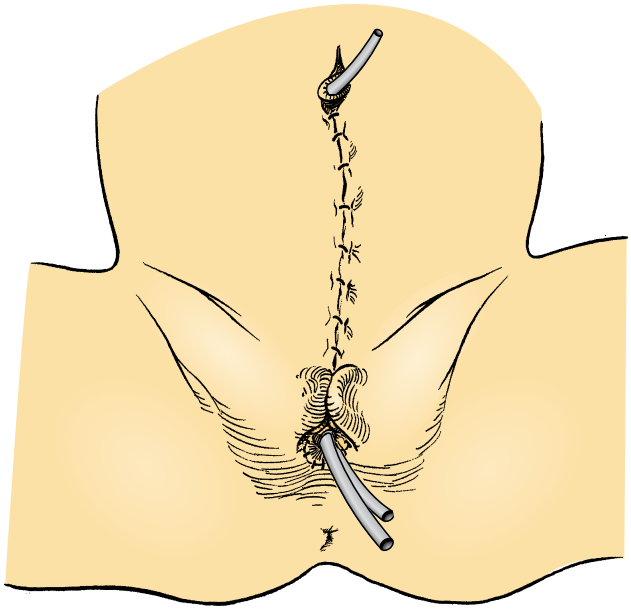

FIGURE 62.35 Skin closure. Denuding the skin medial to the clitoral bodies minimizes the bifid appearance of these structures postoperatively. The labia majora may also be advanced inferiorly to create a more normal cosmetic appearance.

or older had grossly inadequate bladder outlet resistance and either had or will require BNR. This same group also reported on urodynamic findings between patients who had undergone exstrophy repair using a complete primary repair technique compared with a modern stage repair technique. They found that patients undergoing a complete primary repair universally had better bladder stability and bladder compliance than those who had been repaired with a staged technique. Bladder capacity was equivalent between the two groups. Interestingly, patients repaired with a complete repair technique also had normal electromyelography (EMG) results during this study.[160]

Potential Complications and Unique Aspects of the CPRE Repair

Borer and colleagues reported that 75% of 16 males and 29% of 7 females undergoing newborn CPRE required blood transfusion.[160] After CPRE, hypospadias rates have ranged from 50% to 82%.[160,186,196] Borer and colleagues have decreased this rate by using interrupted urethral sutures instead of running ones.[160] Reconstruction of the hypospadic defect can be challenging[160,197] due to the paucity of skin. Hafez and El-Sherbiny have found tubularized penile flap urethroplasty to be superior to Thiersch–Duplay urethroplasty.[197] Bladder neck fistulas have been observed in as many as 41% of CPRE repairs,[198] 78% of which required fistulectomy.

Partial or complete hemiglans and/or corporal loss has been reported by several authors,[198–200] which is likely the most feared complication. Possible contributing factors to this complication include congenitally altered vascular supply, intraoperative use of epinephrine, aggressive dissection and detachment of the corpora and its neurovascular bundle from the ischiopubic ramus and Alcock's canal, and/or diminished arterial perfusion or venous drainage from either corporal kinking, pelvis compression at the time of approximation of the pubic symphysis or corporal rotation, or progressive postoperative edema. This requires aggressive management intraoperatively with relaxation of the symphysis closure. If noted postoperatively, two successful reports of the use of medicinal leeches on the dark glans suggest that the major problem is venous engorgement, suggesting medicinal leeches should be considered for use in this situation.[201,202] However, this complication is not unique to CPRE, as it has been seen in any bladder exstrophy closure method, with a significant number of bilaterally affected cases.[200,203]

Similarly, bladder rupture has been reported in nonaugmented as well as augmented CBE patients, and this complication has been seen in all exstrophy closure methods.[204] While it can be managed nonoperatively with great caution, it can be life threatening and require laparotomy. Contributing factors may include high intravesical pressure and infrequent or incomplete bladder emptying.

Some have criticized the staged approach as requiring a greater number of surgical procedures than CPRE.[203] Given the "relative newness" of the CPRE technique, long-term studies will further delineate the number of patients who require hypospadias reconstruction and BNR to achieve urinary continence. As the male children progress through puberty, phallic growth, presence of chordee, erectile function, and ejaculatory function will be outcomes to closely monitor. Given exstrophy is a complex birth defect to reconstruct, no matter which method is chosen, complications will occur,[199,205] most of which require further surgical interventions.[160]

Radical Soft Tissue Mobilization Technique (Kelly Technique)

The RSTM or Kelly technique has been used at some institutions for decades. The initial contribution by Kelly in 1971[206] described a phallic lengthening procedure performed without osteotomies either at the time of or after exstrophy cystectomy with or without epispadias repair. To lengthen the exstrophic phallus, the crus of each corpus cavernosum is released from the ischiopubic ramus by incising the periosteum of the ischiopubic rami. The crus is completely freed from the ramus but still attached to its neurovascular bundle. Each neurovascular bundle in Alcock's canal is mobilized back to the ischial spine, dividing the obturator internis fascia. This greatly increases mobilization of the corpora such that the original sites of crus attachment can be reattached to the fibrous band connecting the pubic bone.

The RSTM technique to repair CBE (Kelly technique), published from Australia in 1995,[185] described a second stage of the exstrophic bladder reconstruction and epispadias repair without the need for osteotomies. RSTM includes complete separation of the urethral plate from the corpora cavernosa and detachment of the levator ani and urethral sphincter striated muscles from the obturator internis fascia. These voluntary and involuntary sphincter muscles are then wrapped around the tubularized

membranous urethra and bladder neck. The tubularized urethra is transferred ventrally under the corpora, and the urethral meatus is placed as a penoscrotal urethrostomy. In 1995, Kelly reported "physiological continence" in 73% of 19 patients.

The theoretical advantages of the RSTM include a tension-free reconstruction and potentially enhanced continent voiding due to the reconfigured sphincteric muscles independent of the initial severity of or the inevitable worsening of the pubic diastasis. Disadvantages include the need for temporary hypospadias necessitating further penile urethroplasty and the risk of vascular damage to the corpora cavernosa, with partial or complete loss of one or both glans and/or corpora. Several series have reported short- and long-term outcomes. In 2009, Jarzebowski et al.[207] reported the Royal Children's Hospital long-term RSTM outcomes from 1980 to 2007, reflecting the Australian experience. Of 106 CBE patients, follow-up data were available on 44, with continence rates at 70% for complete or partial urinary control. More than half did not require bladder augmentation or clean intermittent catheterization. None of the 9 RSTM females had uterine prolapse, which is lower than the 18% in other published series.[27] The lower abdominal wall was felt to appear abnormally sunken in most adults closed with this technique. In 2015, Varma et al. reported on 38 patients with a 4.5-year mean follow-up; 63.5% achieved complete continence, and 82% had functional continence with no bladder augmentations.[208] Others have also reported successful short-term outcomes with the use of this technique. Complications, such as bladder neck cutaneous fistulas and penile loss, have been reported with the use of this technique.[200,209,210]

Complete Penile Disassembly for the Treatment of Isolated Male Epispadias

Mitchell performed his first complete penile disassembly, or Mitchell technique, for epispadias repair in 1989. Mitchell and Bagli first reported their results in 1996.[187] Complete penile disassembly offers several advantages compared with the modified Cantwell–Ransley technique. The planes of dissection extend anatomically to the bladder neck. This facilitates its use with BNR. Complete mobilization of the urethral wedge from the corporal bodies by disassembly also creates a more normal appearance of the penis by allowing ventral placement of the urethra (Figures 62.36 through 62.38). A detailed description of the surgical technique is included in the "Complete Primary Repair for Exstrophy" section. Zaontz and colleagues reported on a multicenter experience using this technique and found that 16/17 boys had straight erections following repair. Three patients developed pinpoint fistulas, of which two closed spontaneously.[211] Hammouda reported on 42 repairs[212]—glans ischemia occurred in 5 cases, with resolution in 3 and loss of hemiglans in 2 cases. A straight phallus was achieved in 81%, and one pinhole coronal urethrocutaneous fistula (2.4% of patients) was successfully closed. He suggested maintaining ventral vascular attachment of the shaft skin to the urethral wedge, the urethral mesentery, which some have suggested may decrease urethral complications. Perovic has described variants of this technique for epispadias that may be used in selected circumstances as well.[213] Modifications of the complete penile disassembly technique include the use of cavernotomies to assist in the correction of chordee and incomplete separation of the urethral wedge and the corporal bodies to avoid the creation of hypospadias.

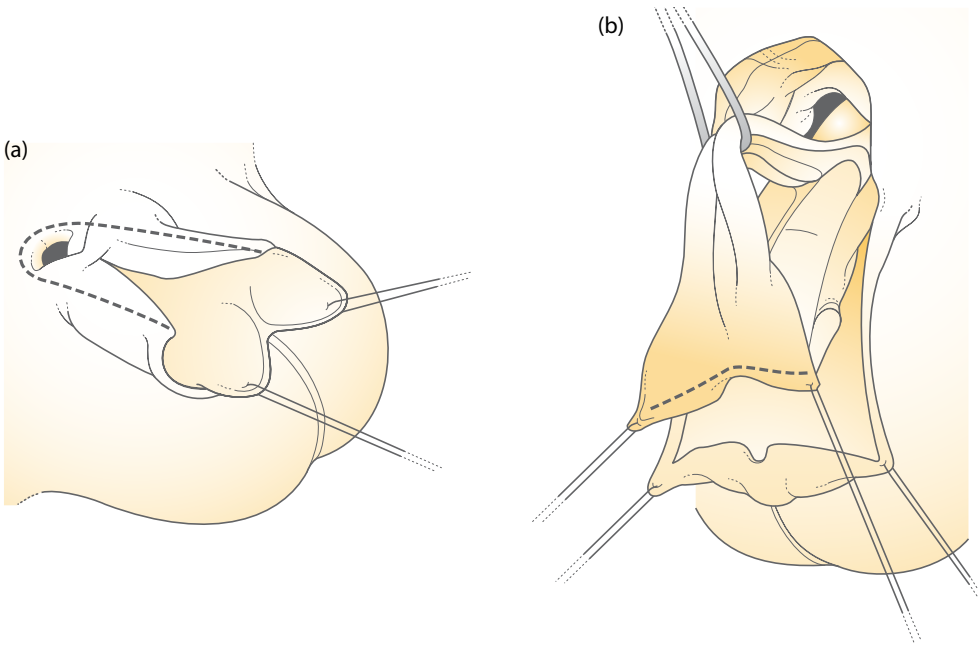

FIGURE 62.36 Complete penile disassembly technique. (a) Lines of initial dissection circumscribing the urethral plate and bladder neck. (b) Careful dissection of the urethra from the underlying corporeal bodies. Dotted line indicates the site of distal incision to free the urethra entirely from the glans. (Adapted from Mitchell ME, Bagli DJ. *J Urol* 1996;155(1):300–4. With permission.)

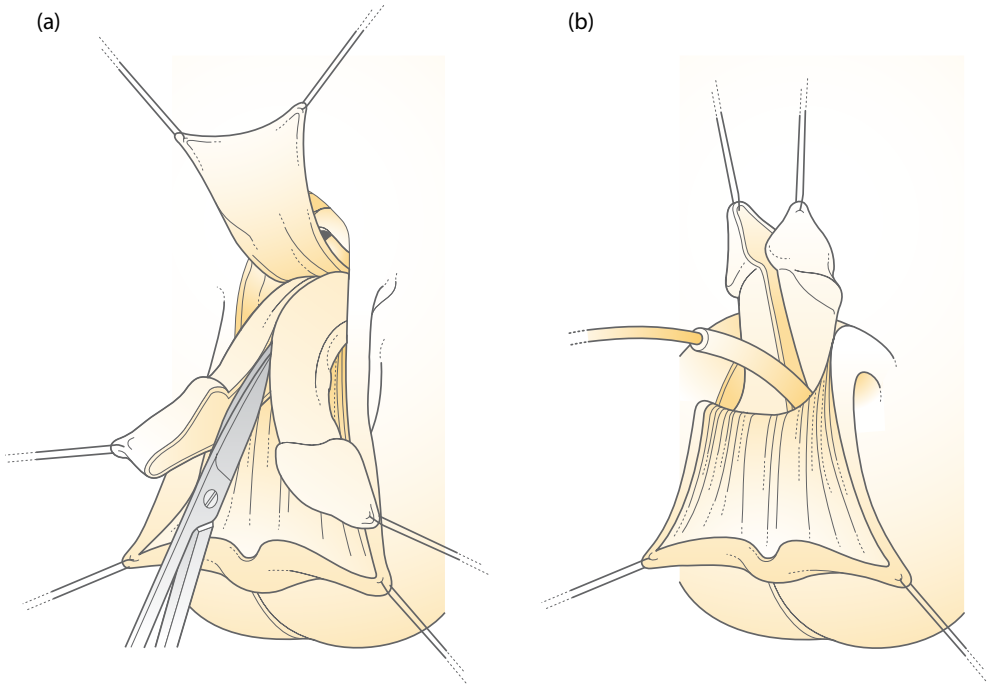

FIGURE 62.37 Complete penile disassembly technique. (a) Corporeal bodies and two hemiglans are separated by a longitudinal midline incision. (b) The urethra is tubularized and brought to the ventrum. The corpora are reapproximated dorsally. They will rotate medially when adequately dissected from each other. (Adapted from Mitchell ME, Bagli DJ. *J Urol* 1996;155(1):300–4. With permission.)

Modern Staged Repair of Exstrophy

The staged reconstruction for exstrophy developed in response to high reported rates of renal damage from single-stage approaches in the 1970s. The initial outline for staged reconstruction as conceived by Jeffs consisted of bladder and posterior urethral closure at birth, BNR at 2–3 years of life, and epispadias repair later.[214] This paradigm was altered when bladder capacity was noted to increase with the added resistance from early epispadias repair.[215,216] Thus, the current MSRE as described by

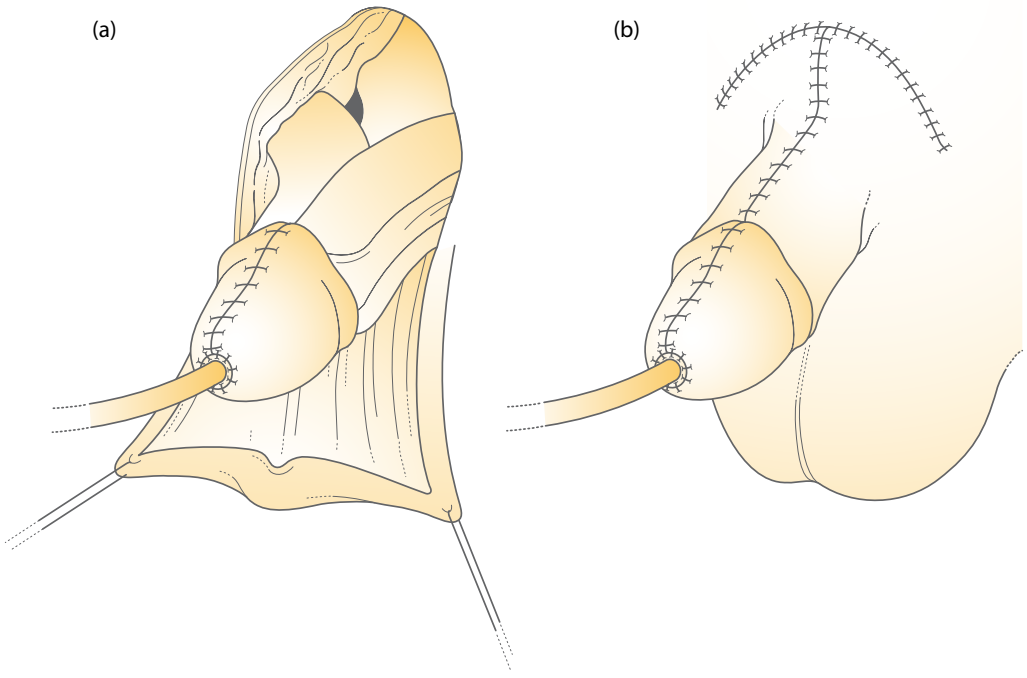

FIGURE 62.38 Complete penile disassembly technique. (a) Completion of urethral meatus; (b) completion of shaft skin coverage. (Adapted from Mitchell ME, Bagli DJ. *J Urol* 1996;155(1):300–4. With permission.)

the Johns Hopkins group consists of bladder and posterior urethral closure at birth or soon thereafter (Stage 1), epispadias repair at 6–12 months of life (Stage 2), and BNR when the bladder capacity is adequate and the child is mentally prepared for toilet training (usually at 4–5 years of life) (Stage 3).[217] In some cases, epispadias repair and BNR ± ureteral reimplantation can be combined.[218,219]

MSRE Stage 1: Initial Early Bladder Exstrophy Closure

At Stage 1 of exstrophy reconstruction, the surgical objectives include (1) closure and repositioning of the bladder and urethra (posterior urethra in males and entire urethra in females) inside the pelvic ring, and (2) approximation of the pelvic ring with closure of the abdominal wall. In male patients, at the end of Stage 1, this closure technique converts the CBE into a male with complete epispadias with incontinence and balanced posterior outlet resistance. This functional state stimulates bladder growth while preserving renal function.

Exstrophy Closure

The initial decision as to whether a bladder template is amenable to closure is currently based on subjective data. Even a small bladder template, if distensible and contractile, can enlarge to a useful size once closed. However, if an examination under anesthesia reveals a small (<5 ccs) acontractile, nondistensible bladder patch, an attempt should not be made to close this bladder.[158] While ureterosigmoidostomy has proven useful in this group of patients,[220] it is preferred to wait and reexamine the child at 4–6 months of age under anesthesia. If at later evaluation the bladder remains inadequate, a nonrefluxing colon conduit is used to divert the urine along with the abdominal wall closure and epispadias repair. This can be converted at a later age to a continent diversion or anastomosed to the rectosigmoid.

If the bladder template is amenable, early exstrophy closure is advantageous for multiple reasons. Socially, for the family, a prompt closure begins the road toward normalcy. In addition, early closure saves the bladder from prolonged exposure, which can lead to such histological changes as acute and chronic inflammation, squamous metaplasia, cystitis glandularis and cystitis cystica, and muscular fibrosis. Functionally, it is likely that this results in a bladder with low capacity and poor compliance.[215] Electron microscopy has shown that the newborn exstrophy bladder is "immature" when compared with control newborns,[221] having fewer small nerve fibers,[14] less smooth muscle, and a threefold increase in type III collagen content.[222] While it is unclear whether these changes are a part of the primary pathology or secondary to the lack of bladder cycling *in utero*, it is conceivable that prompt closure could also "mature" the bladder by restoring bladder cycling. Similarly, clinical data from the Mayo Clinic have verified the importance of immediate postnatal exstrophy closure; infants closed before 7 days of age required fewer bladder augmentations to achieve eventual continence.[223]

Appproximation of the Pelvic Ring

It has become clear that approximation of the open pelvic ring eases abdominal wall closure and diminishes the rate of bladder dehiscence and abdominal wall dehiscence.[224,225] This therefore allows the construction of an intrapelvic urethra and reapproximates the pelvic floor musculature, likely contributing to long-term continence.[36,224] Additionally, in females, osteotomy may reduce the likelihood of uterine prolapse.[224] Therefore, pelvic ring reapproximation is useful at initial bladder closure, as well as at later stages of reconstruction if satisfactory reapproximation was not achieved initially. Pelvic closure in the neonate younger than 48–72 hours old can be achieved without osteotomies due to the effects of maternal relaxin; immobilization is achieved by modified Bryant's traction for 3–4 weeks (Figure 62.15). However, beyond this age or at this time, if the pelvis is not sufficiently malleable, osteotomies are performed at the time of initial closure. An interesting predicament for the surgeon is the situation of the newborn with a large bladder template. In this case, with a bladder having great potential for later continence, the pubic diastasis will be wider and require osteotomy regardless of when closure is attempted. In MSRE with osteotomy, a combined approach of posterior vertical iniac osteotomy with anterior horizontal innominate osteotomy (Figure 62.13) is primarily used with good results.[164,165] Femoral nerve palsy is a possible complication that must be monitored and can be reduced with gradual tightening of the fixator. These osteotomies are secured by intrafragmentary pins, external fixation (4 weeks for newborns, 6–8 weeks for older patients), and light Buck's traction for 2–4 weeks (Figure 62.17).

Male MSRE Bladder and Posterior Urethral Closure Technique

In Stage 1 of MSRE of the male child (Figure 62.39), the bladder and posterior urethral closure technique[1,226] begins as ureteral catheters are placed and secured with a 5-0 or 6-0 chromic suture. These catheters aid ureteral visualization prior to making the initial incision. A traction suture is placed in the glans penis. The posterior urethra is generated by incising a 2 cm wide strip of mucosa from the distal trigone to below the distal verumontanum. Initial dissection begins at the umbilicus and is continued circumferentially, incising around the bladder plate. The entire dissection remains extraperitoneal and is performed with a Colorado tip electrocautery. The two umbilical arteries are ligated and divided. The underlying detrusor muscle is mobilized from the rectus sheath to expose but not enter the peritoneum. The peritoneum is dissected off of the dome of the bladder plate as needed to allow movement deep into the pelvis. Extraperitoneal dissection lateral to the bladder exposes the retroperitoneal space and caudally leads the dissection in the correct plane at the level of the bladder neck. At this level, the rectus fascia meets the pubis and the urogenital diaphragm fibers meet the posterior urethra/bladder neck. The urogenital diaphragm fibers and the intersymphyseal band must be completely taken down from the pubic subperiosteum bilaterally to the pelvic floor, or the posterior urethra and bladder will not be recessed within the deep pelvis.

At this point, the posterior urethra must be assessed. If the urethral groove is adequate in length, no transverse incision is made to transect the urethral plate. If the child has severe chordee and a short urethra that inhibits attempts at penile lengthening, an incision of the

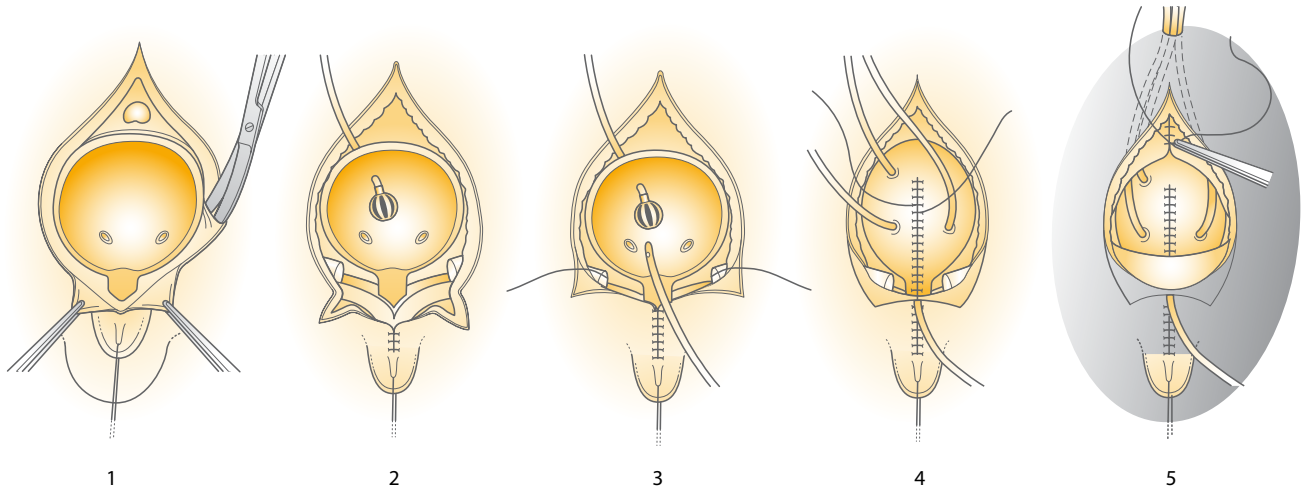

FIGURE 62.39 Primary bladder closure. These diagrams demonstrate the sequence of initial bladder closure in a staged repair for bladder exstrophy in the male patient. From left to right: (1) completion of dissection around the bladder and urethral plate; (2) placement of a suprapubic drainage tube after corporeal reapproximation; (3) tubularization of the urethral plate over the catheter; (4) following two-layer closure of the bladder and urethral plate, the bladder is reduced in the pelvis and fixed with sutures; (5) drainage tubes are brought out superiorly and the fascia, subcutaneous tissue, and skin are reapproximated. (Adapted from Brock III J, O'Neill J. *Pediatric Surgery.* Philadelphia: WB Saunders, 1998, 1709–32. With permission.)

urethral plate may be necessary. Management of this is best assessed after extensive mobilization of the bladder and prostatic plate from the rectus fascia, the pubic bones, and the inferior ramus of the pubis. Once radical division of the urogenital diaphragm fibers from the posterior urethra and bladder neck area is accomplished, the prostatic urethra can be displaced posteriorly into the pelvis. In some cases, division of the anterior attachments of the crura and the suspensory tissue of the penis is needed and displays the gap to be bridged between the prostatic plate and the penile plate. This lack of urethral plate length can be managed by dividing the prostatic plate distal to the verumontanum in a V-shaped fashion. After corporal mobilization and midline reapproximation, the penile urethral plate is fashioned from a lateral rotational flap generated after a single lateral incision into the paraexstrophy skin. Therefore, less tissue redundancy and dissection is necessary. While this has been reconstructed after the manner of Johnston[227] or Duckett,[228] paraexstrophy skin flaps should be used with great caution. The authors have noted a 40% complication rate associated with their use and significant comorbidity.[229]

The corporal bodies are not sewn together at this time, since this will be achieved after the urethra has been transposed beneath the corpora at the time of epispadias closure. Once the dissection appears complete, a sound on the posterior urethra can be compressed and the pelvis manually approximated to roughly assess completeness of mobilization of the posterior urethra and urogenital diaphragm.

After a silicone Malecot suprapubic tube has been placed, the umbilicus is excised and the bladder is closed in the midline in multiple layers with a running 3-0 Vicryl suture. The posterior urethra is also closed onto the base of the penis, sizing it to accept a 12–14 French sound. The intersymphyseal stitch is then placed but initially is not tied. No. 2 nylon suture is recommended. It is key to perform a horizontal mattress closure, planning for the knot to be placed on the anterior surface of the pubis. This technique prevents the suture or knot from eroding into the urethra or bladder neck. Once the suture is in but not tied, three surgical personnel are needed to reapproximate the pubis symphysis. One individual applies pressure over each greater trochanter to push the pubic rami to the midline. A second individual depresses the posterior urethra and bladder neck. The third individual ties the nylon suture. If the rectus fascia is strong, a second No. 2 nylon suture is placed just above the symphysis. The abdominal wall, subcutaneous tissues and skin are then closed in multiple layers. A V-shaped flap of skin is fashioned in the midline for the neoumbilicus at the level of the iliac crests. The neoumbilicus is used as the site to bring the three urinary drainage catheters out to the skin. Inguinal hernias, seen in up to 82% of males, may be surgically repaired at the time of initial exstrophy closure.[40] This can be done through separate incisions or via the midline exstrophy closure incision.

Female MSRE Bladder and Posterior Urethral Closure Technique

In Stage 1 of MSRE of the female child, the surgical technique of bladder, pelvic ring, and abdominal wall closure is identical to that described for the male. However, the closure of the female differs from the male closure in that the female urethra is completely reconstructed at Stage 1.[1,226] The urethral plate mucosal incision is 2 cm wide, traversing from the distal trigone to the vaginal orifice in the female. Paraexstrophy skin flaps are unnecessary in female exstrophy closures.[230] The medial aspect of each hemiclitoris is deepithelialized to permit approximation of the two glans clitori and reconstruction of the mons. The bladder and female urethra are closed in a two-layer Vicryl closure, and the pubic bones, abdominal wall, subcutaneous tissue, and skin are closed as outlined in the male. The monsplasty and genitoplasty are then performed.

Postoperative Care of Stage 1 MSRE

In male and female cases of initial closure, a suprapubic tube and ureteral stents are placed via the neoumbilicus since intubation of the urethra is discouraged. Additional factors that are important to the success of the initial closure include pelvic immobilization and fixation, adequate pain control, prevention of abdominal distention, and postoperative antibiotics.[225,231] The ureteral stents are maintained 2–3 weeks. Adequate urethral caliber and minimal postvoid residuals are ensured prior to removal of the suprapubic tube at 4 weeks. The status of the upper tracts is documented by ultrasound prior to discharge and is followed by ultrasound at 3 months and every 6 months to 1 year. The successfully closed child is continued on prophylactic antibiotics, for essentially all have vesicoureteral reflux. Increasing hydronephrosis, worsening vesicoureteral reflux, retained urine in the bladder, and recurrent UTIs should prompt further evaluation for suture erosion or outlet obstruction. Between the ages of 1 and 3 years, yearly cystograms under anesthesia are performed to assess the degree of reflux and, more importantly, to assess the growth of the bladder. By this age, it is hoped that the capacity will achieve 60–85 ccs.

Delayed Primary Closure

Several recent studies have advocated for the use of delayed primary closure, especially in regard to the use of the complete primary repair technique. Proponents of delayed repair argue that it is safer for the child, and allows a more coordinated surgical effort and time for the most expert team of clinicians to be available to provide surgical care.[232] Others have shown it is feasible to wait months after birth.[233] Zaccara and coworkers used the delay to stimulate the penis with testosterone with the goal to reduce the chance of glans injury and reported good short-term outcomes with this approach in six patients.[234] The successful use of a delayed closure is predicated on adequate protection of the exposed vesical tissue while waiting to coordinate the primary repair. In a series from Mansoura, Hafez showed that delayed use of the primary complete repair technique is also possible in late or initial failed exstrophy closures.[197] A delayed repair does have its disadvantages. Nelson and Gearhart have shown an increased cost, with immediate newborn closure costing roughly two-third that of a delayed repair at their institution.[235]

MSRE Stage 2: Epispadias Repair

Since the initial description by Jeffs of the staged reconstructive approach to exstrophy, the timing of the epispadias repair has undergone change. Originally, Jeffs advocated epispadias repair as the last stage of reconstruction. However, he later recognized that earlier epispadias repair increased the success of later continence procedures by stimulating bladder growth and increasing bladder capacity.[215] In MSRE, epispadias repair (Stage 2) is now typically performed at 12–18 months of age via the modified Cantwell–Ransley technique (Figure 62.40). Epispadias repair can prove challenging. The goals of epispadias repair include a straight penis and urethra, easy urethral catheterization, normal erectile function, and a cosmetically satisfactory phallus. These goals allow the patient to stand while voiding and to have intromission during intercourse.

Preoperative Considerations

In preparation for this repair, the following questions must be addressed: (1) Would preoperative stimulation of penile growth with testosterone benefit the repair? (2) Is penile straightening and lengthening required at this time? (3) Is the current posterior urethral meatus ideal, that is, without and/or not prone to stricture?

Prior to performing the epispadias repair, several surgeons use topical or intramuscular testosterone to increase the size of the phallus and the phallic skin.[213,236,237] Intramuscular testosterone enanthate in oil (2 mg/kg) can be administered at 5 and 2 weeks prior to epispadias closure. The decision as to the need for penile lengthening

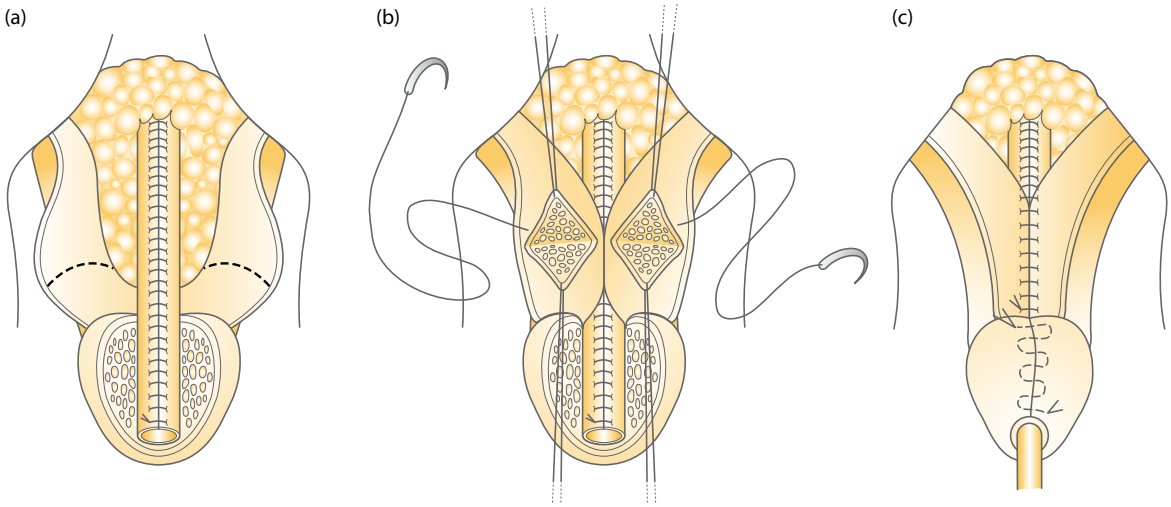

FIGURE 62.40 The steps for the Cantwell–Ransley repair for epispadias. (a) The tubularized urethral plate is placed in a dorsal groove incision in the glans penis. The dotted lines indicate the site of incision for the cavernosa – cavernosotomies; (b) approximation of the corpora cavernosa and performance of cavernosal anastomosis; (c) glans closure over urethra and skin closure. (Adapted from Brock III J, O'Neill J. *Pediatric Surgery*. Philadelphia: WB Saunders, 1998, 1709–32. With permission.)

can then be made after the response to testosterone has been observed. Penile lengthening can be achieved almost always at this time by division of all remnants of the suspensory ligament and scar tissue, as well as further release of the crura from the inferior pubic rami. It is surprising how much of this tissue is intact at the onset of the epispadias repair. In some situations, further urethral lengthening may require free skin grafts, buccal mucosal grafts, ureteral grafts, or pedicle skin flaps. These same maneuvers can be used to repair the scarred or stenosed posterior urethra.

Modified Cantwell–Ransley Technique

Cantwell first described mobilization of the urethra and moving it ventrally for epispadias repair.[238] Ransley subsequently modified this technique and reported on his results in 1988.[239] To begin this procedure, a stay suture is placed into the glans penis (Figure 62.40). A reverse meatal advancement and glanduloplasty (MAGPI) or IPGAM procedure at the distal urethral plate allows advancement of the urethral meatus onto the glans. Following this, skin incisions are made on the lateral edges of the urethral plate and around the epispadic meatus. This plate is dissected from the corporal bodies up to the level of the glans distally and to the prostatic urethra proximally. Glandular wings should be developed distally as well. The corporal bodies are then separated from each other. This allows them to be rotated medially. The urethra is then tubularized over a 6 or 8 French urethral catheter, using a running 6-0 absorbable suture. The corporal bodies are rotated over the urethra and reapproximated using a 5-0 absorbable suture in an interrupted fashion. Cavernocavernosotomies may be performed prior to reapproximating the corporal bodies to help correct persistent chordee. These are performed at the point of maximal angulation. The neurovascular bundles may require mobilization to avoid injuring them if cavernosotomies are performed. The glans wings are then closed over the urethra using interrupted 5-0 absorbable suture. Penile shaft skin can be trimmed and tailored to cover the penis using interrupted 5-0 or 6-0 absorbable sutures. Z-plasties at the level of the pubis may decrease the chance of a dorsal retractile scar at the base of the penis. Postoperative care includes bladder antispasmodics, broad-spectrum antibiotics, and removal of the urethral catheter at 2 weeks.

Outcomes of this technique have revealed urethrocutaneous fistula rates ranging from 5.5% to 42%. In Lottmann and colleagues' series of 40 patients, a successful anatomic and functional result was seen in 90% of the patients at a mean follow-up period of 3 years. These authors also reported complications requiring further procedures in 45%. Complications were more common in those patients who underwent this procedure as part of an exstrophy closure versus isolated epispadias.[240] A recent review of the 10-year Johns Hopkins experience with the modified Cantwell–Ransley procedure[241] found 79 patients with CBE and 14 with complete epispadias: 23% developed early urethrocutaneous fistulas, with a 19% fistula rate at 3 months postoperatively; 7.5% developed urethral stricture proximally, and 83% had a straight urethra by cystoscopy or catheterization; 93.5% had a horizontal or downward-angled penis when standing. Long-term experience with 93 patients with the modified Cantwell–Ransley repair finds a conical glans, a straight penis, and a urethra below the corporal bodies with an acceptable complication rate.[241]

MSRE Stage 1 + 2: Combined Exstrophy and Epispadias Closures

In the event of a significantly delayed primary closure or an initial bladder closure failure, a simultaneous closure of the exstrophy bladder and the epispadias can be performed. The advantages to this approach include one less anesthetic exposure and increasing outlet resistance to stimulate bladder growth. Again, in this scenario, the combined horizontal innominate and the posterior vertical osteotomies are necessary for a secure bladder, abdominal wall, and posterior urethral closure and can allow transposition of the urethra to beneath the corpora with some dissection. This combined approach of simultaneous exstrophy and epispadias closures has been performed in 38 patients at Johns Hopkins with comparable results (i.e., fistula rate, BNR rate, augmentation rate, and continence rate) to age-matched patients who underwent the classic staged approach after failed initial closure.[219]

Bladder Neck Reconstruction: Preoperative Assessment

In incontinent children after CPRE or MSRE, a continence procedure is indicated when (1) the urethra is stricture-free and capable of catheterization if necessary; (2) under anesthesia, the bladder capacity has achieved a minimum volume of 60–85 cc; and (3) the child is mature enough to participate in the postoperative voiding program.[242] This is typically around age 4–5 years. Following a careful history and physical exam, cystourethroscopy and a gravity cystogram under anesthesia are performed for all patients before proceeding to open BNR. Cystoscopy and a gravity cystogram provide information regarding bladder capacity and the status of any previous repairs, including correction of epispadias. Advocates of staged reconstruction emphasize the importance of achieving adequate bladder capacity prior to performing BNR. A bladder capacity of less than 60 mL under anesthesia or during urodynamic evaluation decreases the success of BNR.[32,203] BNR requires adequate bladder capacity because some volume is lost during construction of the bladder neck. Factors that increase the potential for the bladder to achieve adequate capacity prior to BNR include

- Avoidance of urinary tract infections
- Complete bladder emptying with institution of clean intermittent catheterization if bladder emptying is incomplete
- Epispadias repair
- Avoidance of bladder prolapse[43]

Preoperative urodynamic evaluation should be considered because it allows the detection of detrusor hyperactivity or atony, as well as the assessment of functional bladder capacity and leak point pressures. However, the urethra of these patients may be difficult to catheterize. In these situations, a urodynamic catheter can be placed suprapubically

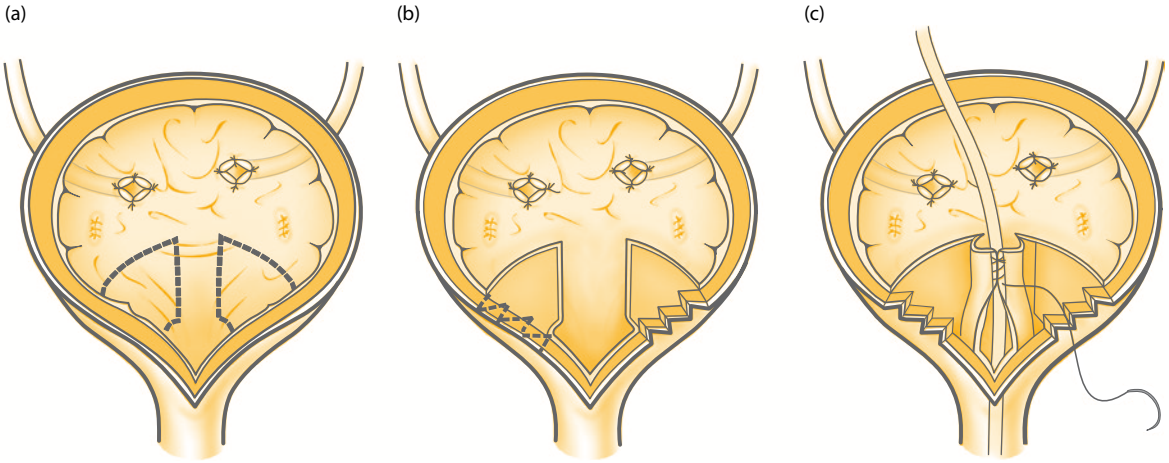

FIGURE 62.41 Principles of the Young–Dees–Leadbetter procedure. This is performed as the third stage of a staged reconstructive approach to exstrophy. The ureters are reimplanted as shown here to prevent vesicoureteral reflux and move them out of the area of the bladder neck reconstruction. The base of the bladder is reconstructed to lengthen the urethra and reinforce the bladder neck. (Adapted from Brock III J, O'Neill J. *Pediatric Surgery*. Philadelphia: WB Saunders, 1998, 1709–32. With permission.)

at the time of the cystourethroscopic examination to be used later that day for the urodynamic evaluation.

Ureteroneocystostomy may be required at the time of BNR to correct vesicoureteral reflux and to move the ureters from the lower bladder where BNR will occur. The Cohen technique is often employed. However, others have described a cephalotrigonal technique that is particularly applicable to exstrophy patients because of the angle of ureteral entry into the bladder.[243] The Marshall–Marchetti–Kranz bladder neck suspension or a bladder neck wrap using rectus muscle or fascia or gracilis may be combined with BNR as well. It is also necessary to reassess whether osteotomy might stabilize the intersymphyseal bar and improve continence at the time of BNR.

The following section describes the most commonly employed BNR techniques, including the modified Young–Dees–Leadbetter (YDL) (Figures 62.41 and 62.42) and the Mitchell (Figure 62.43) repairs.

MSRE Stage 3: Modified Young–Dees–Leadbetter Bladder Neck Reconstruction

The modified YDL bladder neck plasty[244] and the transtrigonal or cephalotrigonal bilateral ureteral reimplantation[243] are the surgical techniques employed in MSRE Stage 3. As evidenced by the name, the combined thoughts of several surgeons spanning over an 82-year period have led to the modern YDL-BNR.[242] To perform a modified YDL procedure (Figures 62.41 and 62.42),[244] the bladder neck is extensively dissected and a vertical cystotomy is made. Occasionally, a portion of the intersymphyseal bar must be resected or the pubic bar divided completely for visual access. After transtrigonal or cephalotrigonal bilateral ureteral reimplantation,[243] a strip of bladder mucosa approximately 1.5–1.8 cm wide and 3–4 cm long is generated and the lateral bladder triangles are demucosalized. Use of an epinephrine-soaked sponge during this dissection aids in hemostasis and visualization. The bladder

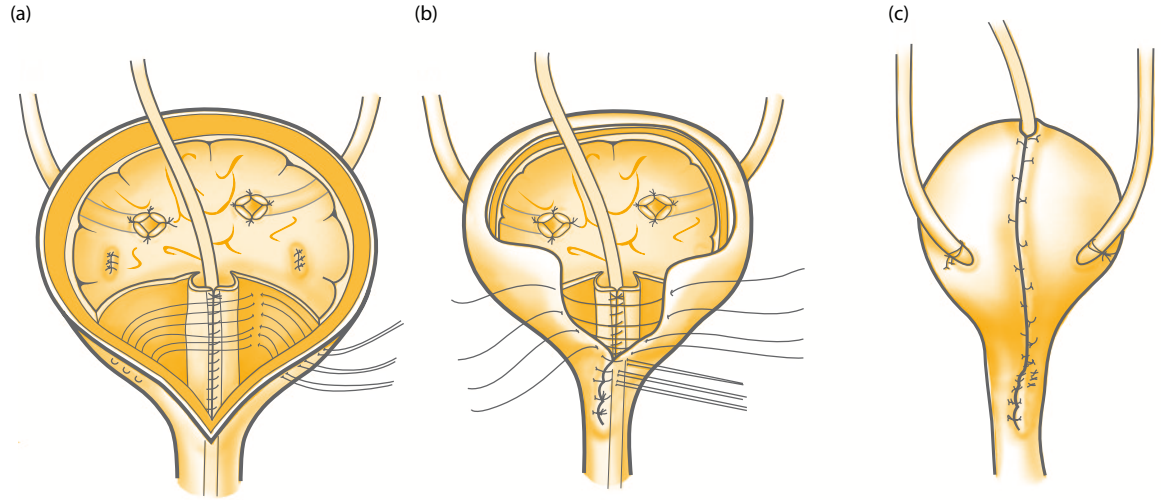

FIGURE 62.42 Principles of the Young–Dees–Leadbetter procedure. The bladder neck closure is reinforced with a pants-over-vest closure. Drainage catheters are brought out superiorly. (Adapted from Brock III J, O'Neill J. *Pediatric Surgery*. Philadelphia: WB Saunders, 1998, 1709–32. With permission.)

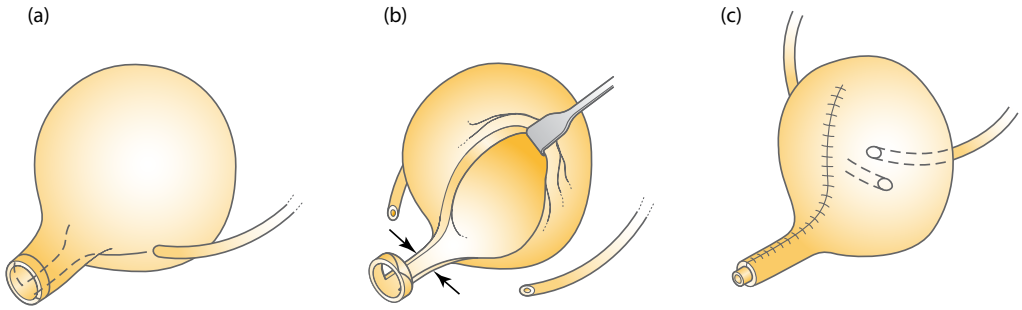

FIGURE 62.43 Mitchell bladder neck reconstruction. (a) Dotted lines represent incisions that will construct posterior bladder strip that will become urethra. (b) Retractor pulling inferior-most portion of the bladder superiorly, effectively enlarging bladder dome. Posterior strip (arrows) is 1.5 cm in width. Ureters detached from bladder. (c) Strip and bladder closed, ureters reimplanted into bladder at high level.

neck may be funneled further with small vertical incisions along the cut edge of the lateral bladder walls. The neourethra is tubularized over an 8 French Firlit stent using interrupted or running polyglycolic acid sutures (4-0 or 5-0). The first of these sutures is a 3-0 PDS, demarcating the bladder neck. The two triangular regions of the demucosalized detrusor muscle are then closed over the mucosal tube in a two-layer "vest over pants" double-breasted technique using 3-0 polyglycolic acid sutures.[43] This reinforces the neobladder neck, decreases the risk of fistula, and augments the outlet resistance.[245] The sutures in the third layer are not cut since they are used in the Marshall–Marchetti–Krantz bladder neck suspension.[242]

In the past, Gearhart has advocated the use of intraoperative urodynamic studies,[246] but now does not routinely perform this. Retrospective studies have shown that intraoperative closure pressures of 70–100 cm H_2O will prevent urinary leakage at 50 cm H_2O intraoperatively.[243] Postoperative management is similar to that following the Mitchell repair. Some surgeons recommend avoidance of a urethral catheter in the postoperative period because of concerns that it may adversely affect later urinary continence. Urinary drainage is achieved by the use of bilateral ureteral catheters and suprapubic tube drainage.[245] Ureteral stents are removed around 2–3 weeks, and voiding trials begin in the third week. The urethra is calibrated with a soft 8 French catheter, and voiding trials are begun with the suprapubic tube in place after the urine has been sterilized. If no urine is passed, cystoscopy and urethral stenting may be required for a short period of time. A bladder readjustment period may span several months before day and subsequently night continence is achieved.

Bladder Neck Reconstruction after CPRE: The Mitchell Repair

This repair employs a modification of the Leadbetter procedure technique described above (Figure 62.43).[244] In this modification, the anterior urethra is incised *transversely and the incision is extended cephalad*. The incision is made full thickness. After cross-trigonal ureteral reimplantation, the urethral strip is tubularized in two layers using a Vicryl or Monocryl suture (4-0 or 5-0) over an 8–10 French urethral catheter, depending on the size of the patient. The bladder may be closed in continuity with the urethral closure. This procedure effectively narrows and lengthens the urethra. It also moves fibrotic tissue at the level of the original bladder neck away from the new bladder neck. Following the closure, dissection around the new bladder neck may be performed if a combined bladder neck wrap or sling will be placed simultaneously.

Postoperatively, urine is drained through a combination of ureteral stents, a suprapubic tube, and a 6 French (Kendall®) urethral catheter. The urethral catheter is removed 7–10 days after the operation. Ureteral stents are removed at 10–14 days after surgery. The suprapubic tube remains for 3 weeks. Voiding trials are performed with measurement postvoid residual urine volumes to assess for urinary retention before removing the suprapubic tube. As with any BNR procedure (without augmentation), several months of adjustment will be required before the patient develops adequate bladder awareness, capacity, and control to achieve prolonged intervals of urinary continence.

Occasionally, trigonal tubularization must be combined with bladder augmentation because of small bladder capacity; most bladder neck repairs decrease bladder capacity since the bladder is used to create the continence mechanism.[247] The stomach offers the best potential to preserve spontaneous volitional voiding in this group, but places these children at risk of hematuria–dysuria syndrome, which can be especially troubling in the face of persistent urinary incontinence and normal sensory innervation.[248] Other intestinal segments may also be used according to surgeon preference. If augmentation is required, appendicovesicostomy or another form of the Mitrofanoff operation can be simultaneously performed if the urethra is difficult to negotiate because of the likelihood that the patient will require intermittent catheterization to empty the bladder after BNR.

BNR Results

After BNR, surgical success is defined as a dry interval of >2–3 hours and spontaneous voiding without catheterization. YDL-BNR and its variants have yielded surgical success with urinary continence rates of 30%–80+% for patients with bladder exstrophy.[244,249–253] Many factors influence the outcome of surgery. For instance, an initial failed bladder closure or prior failed BNR reduces the chance to achieve subsequent urinary continence in these patients.[32] A preoperative bladder capacity of >85 ccs

portends a greater continence rate after YDL-BNR.[254] Use of osteotomies to provide a tension-free anastomosis and patient immobilization through the use of spica casting or Bryant's traction in the postoperative period increases the success of bladder closure and subsequent continence.[218,219] Delayed bladder closure increases the likelihood of eventual need for bladder augmentation due to inadequate bladder capacity that, in turn, reduces the chance for volitional voiding.

Woodhouse and Redgrave have also reported that 8 of 13 patients with initially successful bladder closures and BNR required further surgery in their second decade of life because of poorly compliant, low-capacity bladders that caused urinary incontinence.[255] Surgeons who care for these patients must be committed to the long-term follow-up of this complex group of patients, as late complications may develop. Bauer and Diamond found that only 25% of patients maintained normal detrusor function following YDL-BNR, with compliance and stability being impaired after reconstruction in their series.[256]

Outcomes of MSRE

In contrast to the high rate of renal damage reported by multiple centers employing a single-stage reconstructive effort to bladder exstrophy in the 1970s, results from a staged reconstruction approach appeared significantly better at that time. Jeffs and colleagues reviewed their results with staged reconstruction and noted normal upper urinary tracts in 87%.[257] Later series from Johns Hopkins also achieved low rates of renal damage (12% and 17%, respectively).[224,258]

Urinary continence rates with single-stage efforts in the 1960s and 1970s were also not consistently successful. Continence rates ranged from 0% to 45%, with an average of 17%. In contrast, staged efforts by Jeffs and others demonstrated continence rates of 60%–88% (Figure 62.22).[183,215,225,249,259–262] These results prompted a shift from single-stage reconstruction to planned multiple-stage reconstruction for bladder exstrophy. Accumulation of the data from several series of staged reconstructions reveals that early exstrophy closure, only if in conjunction with pelvic ring approximation, results in a higher rate of continence achieved without augmentation; delayed closure, especially if without osteotomies, resulted in more bladder augmentations.[223,225] Bladder capacity under anesthesia, prior to bladder neck plasty, is the most important single predictor of eventual urinary continence.[21]

Others using the staged approach to exstrophy reconstruction have generally noted lower rates of urinary continence—as low as 9%—with the need for clean intermittent catheterization to achieve urinary continence in as many as 60% of these patients.[244,255,263] These series reflect the variable success of staged reconstruction. Conversion rates in these patients from reconstructive efforts to urinary diversion range from 7.4% to 59.4%.[255,260,264]

Exstrophy Reconstructive Failures

> Errors cannot be avoided. Errors in judgement must occur in the practice of an art which consists largely of balancing probabilities.
>
> *Sir William Osler*

Failed Initial Closure

At the primary closure, failures can manifest as complete bladder dehiscence, bladder prolapse with obstruction, and stricture of the posterior urethra. Failure of the initial closure significantly decreases the chance for eventual continence with volitional voiding.[231,245,265] Gearhart and colleagues reported that only 40% of patients after a failed primary closure attempt will ultimately achieve a bladder capacity adequate for BNR.[243] If more than two closure attempts are required, chances for continence decrease to 20%.[266]

Dehiscence may be largely prevented by approximation of the pelvic ring, adequate pelvic immobilization, prevention of wound infection, abdominal distention, or urinary tube malfunction.[225,231] The child should be given a 6-month recovery period prior to a second attempt at closure. A tension-free closure with osteotomy and immobilization are important factors for both initial and secondary closures.[31] As noted above, the likelihood of obtaining an adequate bladder capacity for bladder neck plasty and eventual continence is markedly diminished following multiple reclosures[31,250,251,267,268]

Bladder prolapse is considered a failure essentially similar to dehiscence and will require bladder reclosure or revision. Prolapse represents dehiscence of the lower end of the closure. It is a consequence of incomplete pelvic ring closure, which is why simple reclosure without osteotomy and pelvic closure is likely to be ineffective.

Bladder outlet obstruction is characterized by postvoid residuals greater than the expected bladder capacity. Outlet obstruction increases the risk of renal damage by raising storage pressures to dangerous levels; this is especially dangerous if unrecognized for several months or more.[41,42] Outlet obstruction also increases the risk of urinary tract infection. The bladder outlet following initial bladder closure may be assessed with sounds or bougies 4–6 weeks after closure to detect stenosis. Ultrasonography of the bladder and upper tracts should be performed 3 months after closure to detect hydronephrosis or bladder distension that might indicate outlet obstruction. Hydronephrosis and high bladder volumes require evaluation with cystoscopy, followed by urethral dilation or the institution of intermittent catheterization as indicated. In a review of 68 patients at Toronto Sick Children's Hospital, 23% developed hydroureteronephrosis following the initial closure, and all were successfully treated with dilation of the bladder outlet or institution of clean intermittent catheterization.[41,42]

Neourethral stricture is often associated with the use of paraexstrophy skin flaps in the posterior urethra;[250,251] pubic suture reaction and erosion or urethral stents have been felt to contribute to this problem. This diagnosis may be somewhat subtle; urinary tract infections, detectable bladder volumes on ultrasound, bladder stones, and prolonged dry periods may be indicators. While nearly all closed exstrophy bladders have vesicoureteral reflux, upper tract deterioration is always due to outlet obstruction. Management options include upper tract diversion (usually diversion into a colon conduit that might be incorporated into augmentation or continent diversion at a later date), urethral dilation and incision, or open urethroplasty

with or without osteotomies, as indicated.[269] Clearly, if renal function is compromised, the therapy must achieve reliable free drainage to allow the upper tracts and the kidneys to fully recover. No additional bladder neck or urethral reconstruction should be performed in the face of an active posterior urethral stricture.

Failed Genital-Urethral Reconstruction

Urethrocutaneous fistula is the most common complication of Cantwell–Ransley epispadias closure, seen in 19% of patients at 3 months postoperatively.[241] Urethral tortuosity with difficult catheterization and strictures are uncommon with this or the Mitchell repair.

At an older age, unsightly penile scars and a short phallus may prompt further surgical intervention. Scar excision can be closed in a plastic fashion if penile skin is available; otherwise, flaps or full-thickness skin grafts can be used. Freeing all scar tissue and suspensory ligament tissue can maximize penile length. A dorsal dermal corporal graft[270] or ventral corporal plication and rotation (Cantwell–Ransley type)[271,272] may additionally help lengthen as well as correct any chordee. However, it must be recognized that the exstrophy penis, when compared with age- and race-matched controls, is congenitally deficient in anterior corporeal tissue as assessed by MRI (Figure 62.3). The posterior corporeal segments, attached to the inferior pubic ramus, are the same length as controls. Therefore, overly aggressive attempts at lengthening the penis may only result in corporeal denervation and devascularization without additional lengthening.[17]

A significantly small phallus can lead to low self-esteem, psychosocial and psychosexual dysfunction, and suicidal ideation. Thus, neophallic reconstruction has been performed, although this procedure is done in a select few centers and with significant risk for complications.[273,274]

Failure to Gain Bladder Capacity

Despite a satisfactory initial closure, some bladders never attain sufficient capacity for normal function. It has become clear that multiple bladder closures, bladder prolapse, dehiscence, bladder calculi, recurrent infections, and vesicostomy have a negative impact on the potential of the exstrophy bladder.[275] Bladder augmentation is recommended in this situation. If the bladder neck and/or urethra is problematic, a catheterizable abdominal stoma with or without bladder neck plasty or transection is performed with the augmentation.[269]

Failed BNR

If urinary continence, defined as a >2- to 3-hour dry interval, is not achieved within 2 years of BNR, this is considered a failure. "Voiding" for an individual with exstrophy is passage of urine against a relatively fixed resistance and thus is not exactly normal.[276,277] Patients who fail to achieve continence after BNR should undergo urodynamic evaluation. Some patients will demonstrate detrusor underactivity,[278] stable detrusor,[279] or uninhibited bladder contractions resulting from increased resistance at the bladder neck after reconstruction. Treatment with anticholinergic agents such as oxybutynin can significantly improve the continence of these patients. If urodynamic evaluation reveals a bladder with adequate capacity but low leak point pressures, the YDL procedure can be performed again. Some success has been seen in repeating a YDL repair if the bladder neck is patulous and the bladder capacity is adequate.[280–282] However, this is an unusual occurrence. The majority of bladder neck failures have inadequate bladder capacity and require eventual augmentation or a continent diversion.[31,32,229] Either the bladder neck is transected proximal to the prostate with a Mitrofanoff substitution or a continence procedure is performed, such as artificial sphincter[283,284] or injection of bulking agents.[230,281,282,285]

Delayed urinary continence has been reported by Kramer and Kelalis at the onset of puberty in some males and has been attributed to prostatic growth.[286] By MRI, the prostate of exstrophy patients is clover shaped and absent anteriorly, while its mean weight, maximal cross-sectional area, and volume are normal.[21] Therefore, it is doubtful that growth of this abnormally configured prostate can impact urinary continence, although the experience of improved continence at puberty is not uncommon.

Recently, autologous myoblasts or muscle-derived cells have been injected in incontinent epispadias–exstrophy patients with mixed success.[287–289]

Management Alternatives after Failed BNR

After failed BNR, several other options are available.

Artificial Urinary Sphincter

An artificial urinary sphincter may be used to achieve urinary continence in patients who have adequate bladder capacity and compliance but an incompetent bladder neck after BNR.[284] This device preserves the ability to volitionally void, but because of the requirements for later revision and the dexterity required to use it, it is not our first choice for younger patients. Others have described its use in combination with bladder augmentation. In one series of 11 patients who underwent sigmoid augmentation with artificial urinary sphincter placement, 9 are continent. However, these patients required multiple operative revisions to achieve this degree of continence.[290] Sphincter erosion into the bladder neck or bowel segment can also occur, possibly due to prior surgeries of the urethra and bladder neck.[291]

Bladder Neck Wraps and Slings

Bladder neck wraps and slings may also be used. However, other series reporting on the use of bladder neck wraps suggest that this procedure does not consistently maintain long-term urinary continence, especially in male patients, who constitute the gender majority in exstrophy.[224,225]

Bladder Neck Bulking Agents

Several authors have used collagen injections[230,292,293] and, more recently, dextranomer (Deflux™)[294–296] at the bladder neck to treat patients with stress incontinence after BNR or primarily in mildly affected epispadiac patients. Ben-Chaim et al. reported an improvement in continence in 53% of patients after collagen therapy, although most required multiple injections.[230] Since this injection

is placed into a previously operated field, overall success rates for bladder neck bulking agents are significantly less than the success rates achieved for vesicoureteral reflux (in children without exstrophy).[297] Bulking agents can be used as an adjunctive procedure for those patients who demonstrate slight leakage due to stress incontinence after BNR.

Bladder Neck Closure

Bladder neck closure in conjunction with appendicovesicostomy is also an option in those patients who have failed multiple attempts at BNR. This option eliminates the chance to void per urethra and commits the patient to intermittent catheterization. It is difficult, if not impossible, to reverse.

Urinary Diversion

Proponents of urinary diversion for the treatment of exstrophy argue that the varying continence rates achieved with functional reconstruction demonstrate the unreliability of this approach.[298] The use of the native bladder will often require later bladder augmentation with intestinal segments to achieve a functional bladder storage capacity. Certainly, some centers report poor rates of continence after primary reconstruction, and some urodynamic studies do demonstrate low urine flow rates and poor contractility in patients following primary bladder reconstruction.[299,300]

Primary urinary diversion avoids the complications associated with functional reconstruction, including urinary retention and subsequent kidney damage, a predisposition to urinary tract infection, and later dependence on clean intermittent catheterization to empty the bladder with its own possible complications of urethral stricture formation, epididymitis, and urinary tract infection.[301] Advocates of early urinary diversion also cite a decreased risk of epididymitis and obstruction of the vas deferens by the creation of a seminal receptacle with a suprapubic window at the level of the prostatic urethra.[301] Diversion can be combined with cosmetic operative procedures for the external genitalia.

Urinary diversion is used to provide urinary continence in patients who have failed multiple attempts at functional reconstruction.[302] Some also advocate primary urinary diversion for patients with bladder plates deemed too small to close. However, because it is impossible to *accurately predict* which bladder plates will increase significantly in size after primary closure, we *do not* divert the urine primarily in exstrophy patients. Arap has described preserving the very small bladder by using it as the continence mechanism rather than a storage vessel after anastamosing the ureters to a sigmoid conduit in an antireflux manner.[359] Final reconstruction involves attachment of the sigmoid conduit to the neourethra and reconstruction of the abdominal wall.

Advocates of early urinary diversion argue that it achieves the primary goals of surgical intervention for bladder exstrophy with fewer operations and higher success rates than are achieved with bladder closure and urethral reconstruction. Prior to the popularization of staged reconstruction, ureterosigmoidostomy was the treatment of choice for exstrophy reconstruction. The long-term complications of ureterosigmoidostomy, including hyperchloremic metabolic acidosis, chronic pyelonephritis, and a 250- to 500-fold increased risk of colonic adenocarcinoma formation at the site of anastomosis dampened enthusiasm for this procedure despite improvements in ureteroenteral anastomoses.[303–306] Ureterosigmoidostomy was subsequently replaced by incontinent urinary diversions, such as the colonic and ileal conduits, which have the disadvantage of an external appliance. The introduction of clean intermittent catheterization allowed the development of continent urinary diversions, which are now the preferred method of urinary diversion to the abdomen in this population.

Rectal Reservoirs

Various investigators have made significant improvements on the use of the rectum as a urinary reservoir, including the Mainz II pouch and the sigma pouch.[298,301] Use of a rectal reservoir permits urinary continence without reliance on clean intermittent catheterization. Hohenfellner and Stein report a 92% rate of renal preservation in their series of children treated primarily with a urinary rectal reservoir (Mainz II pouch since 1991). Continence rates of 97% in school-aged children are reported in using this technique.[301] The Heitz–Boyer–Hovelaque procedure involves isolation of a rectal segment for ureteral implantation, followed by posterior sagittal pull-through of the sigmoid colon through the anal sphincter to achieve both urinary and fecal continence with separate anal openings for each. A small series using this procedure reported continence rates of 95% with acceptable complication rates.[307] The modified Heitz–Boyer–Hovelacque rectal bladder at 5–10 years' follow-up showed continence, except minor urine loss at night; few to no UTIs, and excellent renal function in 14 children[308] and in 19 children.[309]

Complications of rectal diversion include fecal–urinary incontinence in patients with impaired anorectal sphincter control.[245] Metabolic electrolyte imbalances can be treated with complete frequent emptying of the rectal reservoir, reducing the contact time between urine and the absorptive mucosa, along with oral bicarbonate replacement. Oral bicarbonate replacement is recommended for all patients who have a base deficit of 2.5 mmol/L or greater.[301] The risk of malignant degeneration still remains with use of a rectal urinary reservoir. If the increased risk of adenocarcinoma is due to conversion of urinary nitrates into carcinogenic nitrites by fecal bacteria, modifications of the rectal reservoir to prevent admixture of feces and urine may theoretically decrease the incidence.[310] Long-term results are not yet available.

Approaches to Urinary Diversion

Methods to construct urinary diversions include the following.

Continent Diversions

External diversions (continent urinary reservoir)

- Indiana pouch
- Mainz pouch
- Penn pouch

- Kock pouch
- Others

Internal diversions (rectal sphincter-based continence)

- Ureterosigmoidostomy
- Sigma pouch
- Ghoneim reservoir
- Gersuny
- Heitz–Boyer–Hovelacque procedure
- Rectal bladder with proximal colostomy
- Ileocecal ureterosigmoidostomy

Incontinent Diversions

- Ileal conduit
- Colon conduit
- Ileocecal conduit

Management of Cloacal Exstrophy

Introduction

Although CE has been recognized for at least several hundred years, Spencer was the first surgeon to report the successful repair and survival of an infant with this anomaly in 1965.[311] Mortality rates of infants with CE remained high for years following this initial success. In 1979, the mortality rate of a contemporary series stood at 50%.[312] Affected infants routinely died of malnutrition and sepsis. With continuing improvement in total parenteral nutrition and neonatal management, mortality rates currently are less than 10%.[313] Issues of quality of life are now paramount in this patient group.

Perioperative Management

CE patients are best cared for by a team of experienced physicians, including a pediatric urologist, surgeon, orthopedist, gastroenterologist, endocrinologist, and neurosurgeon. Given many are diagnosed prenatally by ultrasound, this multiorgan system care can often be coordinated prior to the infant's birth. Advances in neonatal care, intravenous nutrition, and the surgical management of these children have markedly reduced the mortality and morbidity of this disease. Nonetheless, the management of these children remains challenging.

In the neonatal period, the bladder and hindgut plate should be covered (Saran Wrap or Vigilon) to protect these structures. The umbilical cord should be ligated with a silk suture to prevent an umbilical clamp from abrading the bladder or hindgut plate. Antibiotic prophylaxis should be given to these patients because of the high incidence of renal abnormalities.

Preoperative studies include ultrasonography, abdominal x-ray, and karyotyping. Sonographic examination allows the evaluation of the upper urinary tracts, internal genital structures, and spinal cord. Because the genital anomalies associated with CE may make it difficult to accurately identify the sex of the baby (Figures 62.8 and 62.44), karyotyping is indicated to define the chromosomal sex in situations where the gender of the infant is unclear.

FIGURE 62.44 Female cloacal exstrophy. When compared with male cloacal exstrophy in Figure 61.8, each hemiclitoris is not much smaller than each hemipenis. However, closer inspection reveals labia majora instead of bilateral rugated hemiscrotum. The vaginal orifices cannot be seen in this view, but are present.

Cloacal Exstrophy Closure Techniques

Each CE patient is unique, requiring an individualized surgical plan. As indicated above, closure of a CE should involve a team of pediatric specialists experienced in the care of these children. If the baby is medically stable, the initial reconstructive procedures should be performed within the first 48 hours of life, thus taking advantage of the pliable bony pelvis if closure of the entire defect is possible. However, in 29%–75% of these children, spina bifida is present and may need surgical intervention, delaying the ventral abdominal wall closure. In addition, the omphalocele, seen in 88% of CE patients,[314] may require immediate care to prevent rupture. The size of the omphalocele, the size of the hindgut plate and bladder plates, the extent of the pubic diastasis, and the extent of comorbidities largely dictate the timing and staging of the initial closure. A large omphalocele containing liver may preclude any attempt at complete closure.[26] If the large omphalocele is not closed because of increased abdominal pressure or tension, a silastic silo closure may be used as a delayed closure of the abdominal hernia, or an alloderm graft can be used to complete the closure.

Gastrointestinal issues are paramount. Although in the past a terminal ileostomy was routinely performed, the metabolic consequences can be significant. Currently, management decisions focus on the use of the exstrophic cecal plate and the terminal blind-ending hindgut. Options for the cecal plate include retaining it in the bladder closure as a bladder augmentation versus separating it and reconstructing it for the fecal stream. To improve bowel length and water resorption, most recommend that the cecal

plate be tubularized, making the terminal ileum, cecum, and blind-ending hindgut segment all in line for the fecal stream. The hindgut segment can be anastomosed in either an isoperistaltic or antiperistaltic fashion and brought out as the terminal colostomy. In some cases, there are hindgut duplications. No segment of bowel should be discarded unless absolutely unusable, since it could be used in reconstruction of the bowel, bladder, or vagina. Similarly, appendiceal segments should be preserved in these patients for possible use in later reconstruction of the urinary tract. Few patients with CE are candidates for an anal pull-through procedure. The best candidates are children with anal fistula and preserved innervation.

Before the dissection begins for bladder closure, ureteral catheters are placed in the ureteral orifices and secured in place with a 5.0 chromic suture. The omphalocele repair is begun with the initial dissection beginning superiorly. The umbilical vessels are ligated and the bladder plates separated from the adjacent skin, as described in the CPRE and MSRE techniques. The medial cecal hindgut plate is separated from the paired, separated bladder plates and tubularized. After the hindgut has been reconstructed, the bladder halves are reapproximated in the midline. Inguinal hernias should be repaired if detected. Primary bladder closure may be performed at this time if the intra-abdominal pressure remains low after omphalocele closure. This can be determined clinically by assessing ventilatory effort. A one-stage closure of CE, including closure of the omphalocele, cecal plate tubularization and hindgut terminal colostomy, bladder and urethral closure, reconstruction of the external genitalia, and osteotomies, should be performed only under optimal anatomical conditions. The decision to proceed with one-stage closure versus staged reconstruction spanning a period of months must be weighed carefully. Following forced closure, increased abdominal pressure may result in organ ischemia, excessive tension to the midline closure, or compromised lower extremity blood flow. The importance of including surgeons experienced in the care of these patients cannot be overemphasized. Thus, the reconstruction can be staged at this point by converting the CE (Figures 62.6 and 62.44) into a CBE (Figure 62.45). A colostomy is created with the previously described caveats in mind.

If staging was required, once the baby has recovered sufficiently to tolerate another surgical procedure, the remaining steps of reconstruction of the bladder, bladder neck, and genitalia using the CPRE technique[315,316] or MSRE technique[317] are performed as previously described. Deep pelvic diaphragm dissection with division of the intersymphyseal band is crucial to allow for appropriate posterior positioning of the bladder and urethra. After the bladder and urethra are positioned within the pelvis, reconstruction of the bladder, genitalia, abdomen, and pelvis is anatomic.

Osteotomies are almost always necessary to assist in closure and posterior positioning of the urinary tract, given that the pubic diastasis is usually more severe than in CBE. Prior to incision, the need for osteotomies is assessed under anesthesia by watching for ischemia of the lower extremities and external genitalia during pubic reapproximation. The Hopkins group recommends bilateral combined anterior innominate and vertical iliac osteotomy

FIGURE 62.45 Staged closure of male cloacal exstrophy. The omphalocele has been reduced. The cecal plate had been tubularized and the terminal hindgut has been brought out as an end colostomy. The hemibladders have been united in the midline but remain exstrophic.

with gradual approximation of the bones over 1–2 weeks via the external fixture and interfragmentary pins.[37,318] The Seattle group prefers iliac osteotomies. Other authors prefer to avoid the use of osteotomies because they believe that osteotomies make the abdominal closure more difficult.[319] This has not been our experience. Fewer wound dehiscences and ventral abdominal wall hernias have been noted with osteotomies.[37]

Late procedures may be required on the urinary tract to achieve continence, including BNR; bladder neck closure; bladder augmentation with stomach, ileum, or hindgut; and creation of a continent catheterizable stoma.[50,267,268,320,321] Given that nearly all these children will be dependent on clean intermittent catheterization to achieve dryness, surgical reconstruction must be individualized to meet the needs of their limitations.

Genital Reconstruction and Sex of Rearing

Sex assignment for patients with CE is currently under scrutiny both by the medical profession and by the lay public. Traditionally, male patients underwent sex conversion in infancy because of concerns that the small, paired male hemiphalluses in these patients were inadequate for reconstruction. This approach was supported by anecdotal data of unsatisfied patients following reconstruction of the male phallus.[50] These observations, in conjunction with the prevailing notion that humans were gender neutral at birth and could undergo sex conversion safely in infancy, have recently come into question.[186,322,323] Recent evidence suggests that gender imprinting may occur during fetal development.[324] Gender identity now appears to be a much more complex issue than previously thought.

Currently, males with CE are routinely reconstructed as males whenever technically possible. Many gender reassigned individuals will later identify themselves in a male gender role in adolescence and adulthood.[186,322,325] Technically, however, reconstruction of external male genitalia in the CE population can be quite difficult. The wide

pubic diastasis and small phallic size add to the technical complexity because these findings make it more difficult to bring the two phallic halves together in the midline. In some cases, if one phallic half is diminutive, the small one can be removed and the reconstruction performed using only the larger phallic half.

Female genital reconstruction is complex as well. In genetic females, complete Müllerian and vaginal duplication often leads to attempted midline reapproximation. However, if one system appears more substantial, excision of the lesser unit may be prudent. In genetic males raised female, neovaginal reconstruction is typically delayed and may require use of hindgut segment or perineal skin.

Gastrointestinal Reconstruction

Short-gut syndrome is usually present in patients with CE at birth, even in those with normal length of bowel. The effects of malabsorption and fluid loss from this entity appear to be clinically most significant early in life.[326] Many such children require parenteral nutritional support in early infancy.[327,328] Because of this, we share the belief that the hindgut should be constructed and placed in continuity with the intestine during initial reconstruction. This will perhaps improve nutrition and also preserve intestinal tissue that may be used in later reconstruction of the urinary tract or to form a vagina, if this is eventually needed. It is interesting that Rickham noted the importance of preservation of the hindgut in the intestine in his report of the first surviving neonate with CE.[329]

Long-Term Concerns in Exstrophy

Psychosocial Concerns

Children with exstrophy face significant challenges in the development of their psychosocial identity.[330] Unfortunately, this area of development has been poorly studied but is drawing attention.[331] Reiner and coworkers have noted that "in children with exstrophy, psychosocial and psychosexual hurdles are the rule" rather than the exception. A preliminary study of 135 children and adolescents with bladder exstrophy revealed that a detailed sexual and social history was rarely part of the routine evaluation of these children. Other studies have shown that adolescent males with exstrophy were psychosexually delayed 2–4 years compared with their peers and delayed 4–6 years in their activity. Data on teenage girls with exstrophy are incomplete, but Reiner has noted that these girls struggle with sexual self-esteem issues, such as body image, genital perception, and genital appearance. Current recommendations include regular assessment of social development. These may include child psychiatric evaluation at birth, with parental education about concerns. Child assessment can begin as early as 12–18 months of age and then periodically after that. Evaluation and intervention are also useful prior to operative procedures. Reiner has found that anxiety and psychosexual disorders are universal in the patients he has evaluated to date. Further, a higher percentage of patients with exstrophy experience suicidal ideation.[332] Routine patient and parental education should be considered.[333] A recent German study found affected females to have better psychosocial and developmental outcomes than affected males.[331] Adolescents with exstrophy are resilient, however, and have been shown to develop creative coping strategies to deal with the chronic aspects of their condition.[330] Most adolescents with exstrophy express a strong desire to be normal and resent arrangements that emphasize their differences (such as the use of faculty or nursing facility bathrooms).[334]

Sexual Function

While sexual function is of little relevance to the newborn or prepubertal child born with exstrophy, it is an issue of considerable importance to the parents of the child, who wonder what future sexual function will be possible for their child, and for adolescents with exstrophy, for whom sexual function or the potential for sexual function is an area of focus.

For male patients, erectile function and sensation are usually intact.[335,336] Variable degrees of chordee can create difficulty in achieving intercourse for some patients.[336] Libido for patients with exstrophy is characteristically present with or without surgical correction. However, penile size and curvature can impact the ability to engage in sexual intercourse. Several studies of adult men with exstrophy have demonstrated that approximately a third choose not to or cannot engage in sexual intercourse.[306] Woodhouse noted in his series of patients with exstrophy that many of them do develop stable partnerships. He found 33 of 43 patients married or living with a partner. However, sexual counseling in these patients is paramount because of the difficulties they face. In these situations, a female superior position provides closer apposition of the genitalia for intercourse.

For some men, exceedingly small penile size deters them. Several groups have published the successful use of a radial forearm flap to construct a penis analogue in five men with diminuitive penises.[274,337] All described improved quality of life following the operation.[273,338–343]

Ejaculation is often present as well despite the extensive reconstructive procedures that are done for these patients. The seminal emission may be slow and continue several hours after orgasm. Further, sperm quality and quantity are often impaired. This may be due to partial obstruction from surgery or epididymitis or recurrent urinary tract infections. In the Hopkins series, only 63% had antegrade ejaculation.[25] However, long-term studies in adults with exstrophy found that a minority of them were able to conceive without ARTs, while others used ARTs to have children.[306,344,345]

For women with exstrophy, ~80% will require genital surgery,[27] including vaginoplasty, to permit intercourse, or clitoroplasty or labioplasty.[346] Diminished clitoral sensation and partial clitoral atrophy have been reported.[346,347] Sexual intercourse is possible, and sexual function is often intact.[335] Of 38 bladder exstrophy females who had tried to conceive, 66% had been successful.[348] In Woodhouse's series, 14 of 23 patients had normal intercourse,[349] while 18% reported dyspareunia in the Hopkins series.[27] Narrowing at the vaginal introitus can be problematic in up to 32% of patients.[350] This can be addressed with serial calibration and dilation as a first option or with vaginal cutback or advancement skin flaps as surgical options. Some recommend the use of vaginal dilation postoperatively,

but it is not mandatory. Fertility is unimpaired in female patients with exstrophy, although prolapse occurs in 38% secondary to the lack of pelvic floor support structures and can be unmasked with vaginoplasty or pregnancy.[28] This can make bed rest necessary in the later stages of pregnancy. Pregnancy in a patient with exstrophy is considered a high-risk event,[97,351] and many pregnancies have been reported with deliveries vaginally or by Caesarian section.[27,352] Hydronephrosis and bacteriuria are common during pregnancy and may necessitate antimicrobial prophylaxis.[353] Caesarian section is the recommended path of delivery (with urologic presence) versus vaginal delivery, which can occasionally be problematic.[348,354] Vaginal and cervicouterine prolapse surgery may be necessary in women with exstrophy, as prolapse occurs at a younger age than in the general population.[28,352,355] Several surgical methods (colposuspension, mesh sacrocolpopexy, uterine antefixation, and Gore-Tex uterine wrap) have been reported in exceedingly small numbers; however, the best method of repair has not emerged.[356] For recurrent prolapse cases, simultaneous osteotomy with external fixation has been successfully employed.[30]

CONCLUSIONS

Whereas it was once deemed "impossible to restore the bladder" (H. J. Jewett, patient communication, 1957) in patients with exstrophy, modern management can successfully preserve renal function, provide urinary continence, and maintain the health of children and adults with bladder exstrophy and CE. The progress made over the past few decades makes us optimistic in anticipating the future of therapy for these interesting and vital patients.

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CHAPTER
63

Unusual Conditions of the Bladder, Including Bladder Trauma, Urachal Anomalies, and Bladder Diverticula

Pablo Gomez III and Marc Cendron

INTRODUCTION

Other than the notable embryological pathologies of the bladder, which include bladder exstrophy and cloacal anomalies, anomalies of the bladder in children are relatively rare. In this chapter, a brief review of the embryology and function of the bladder is presented, followed by a review of bladder trauma, bladder diverticula, and urachal and other unusual bladder entities, such as bladder agenesis or hypoplasia, bladder duplication and septation, and megacystis, as well as tumors and inflammatory conditions seen in children.

The embryology of the bladder is a complex, three-dimensional process that encompasses the formation of the cloaca (or primitive hindgut), as well as the elaboration of an anteriorly located muscular reservoir connected to the ureters posteriorly and to the urethra inferiorly.[1] At about 28 days of gestation, the cloaca undergoes partitioning by ingrowth of the mesoderm from the point of confluence between the allantois and the hindgut to form the urorectal septum, which will separate the genitourinary tract from the gastrointestinal tract. The urogenital sinus thus formed will divide by further ingrowth of the mesoderm to form the bladder precursor anteriorly and superiorly during the fifth and seventh weeks of gestation. The bladder is connected to the allantois and the mesonephric ducts. Growth of the anterior abdominal wall will allow expansion of the bladder. The allantois, which later will become the urachus, remains attached to the bladder dome and extends to the base of the umbilical cord. The lumen of the urachus will obliterate early in human fetal development.[2]

Structural organization of the bladder occurs at 16 weeks of gestation, with histological appearance of urothelium by 20 weeks of gestation concomitant with organization of smooth muscle cells into three layers. Organization of the bladder therefore depends on the carefully orchestrated differentiation and growth of the mesodermal mesenchyme. While the exact molecular events involved have not been clearly and precisely elucidated, functional organization of the bladder has been well identified on a histological basis. The bladder begins to provide storage and expulsion functions as the kidneys start to produce urine at 9–10 weeks of gestation. The muscular and urothelial units are submitted to sequential stretching and contraction as documented by prenatal ultrasonography.[3] Developmental alterations in the structural organization of the bladder may allow for anomalies such as bladder diverticula to occur. In this case, normal muscular organization of the paraureteral area is altered to the extent that a muscular defect occurs, allowing for the urothelium to herniate through it and into the perivesical space.

Bladder agenesis in viable newborns is exceedingly rare and mostly observed in females.[4,5] The exact cause of bladder agenesis has not been determined. In general, the gastrointestinal tract is intact, implying normal division of the cloaca with atrophy or failure of the bladder to develop, resulting in the incorporation of the distal ureter into the urethra, vestibule, or Gartner's duct in the female and the prostatic urethra in the male.[6] The ureters may display distal obstruction due to their ectopic location, causing upper urinary tract dilatation and possibly poorly functioning, dysplastic kidneys. The outcome for these patients depends largely on their renal and pulmonary function. Most infants born with bladder agenesis are stillborn, and rare survivors are usually females.[7,8] Initial urinary diversion followed by major reconstruction of the lower urinary tract may be required should renal and pulmonary function be sufficient for survival. Other congenital anomalies are frequently seen in association with bladder agenesis.[9]

Conditions associated with under- or overfilling of the bladder with urine (cycling) early in development may lead to either underdevelopment of the bladder (hypoplasia) or overdistention (megacystis). Bladder hypoplasia occurs in disorders in which either low urine output causes the bladder not to cycle adequately (seen in bilateral renal agenesis or severe bilateral renal dysplasia), low outlet resistance (as seen in epispadias with incontinence), or if the bladder is bypassed altogether (bilateral ureteral ectopia). Children who experience chronic low urine output due to renal failure or due to bilateral nephrectomies may develop acquired hypoplasia of the bladder. This condition is usually

reversible once the child has undergone renal transplantation, increased urine output and bladder cycling. A pretransplant voiding cystourethrogram (VCUG) will show small bladder capacity, and very often filling of the bladder will be associated with benign, self-limited extravasation of contrast (Figure 63.1).[10]

Congenital megacystis, or enlarged bladder, can be seen in association with refluxing, massively dilated ureters, a syndrome known as megacystis–megaureter (Figure 63.2).[11] The dynamics of the dilated bladder and refluxing urine cause a constant cycling and concomitant overdistention (yo-yo effect between the upper and lower urinary tract). Prenatal diagnosis of this rare condition has been reported.[12] Congenital enlargement of the bladder is also reported in association with microcolon intestinal hypoperistalsis syndrome and Ehlers–Danlos syndrome, and it can also be secondary to bladder outlet obstruction.[13,14] Initial management of patients with megacystis is directed toward improving bladder emptying and often requires clean intermittent catheterization and antibiotic prophylaxis in order to prevent infections. Surgical treatment of the vesicoureteral reflux should, in general, be delayed until 6 months of life. Reimplantation of the ureters (with or without tapering) may be helpful in improving bladder dynamics and emptying of the upper urinary tract. Reduction cystoplasty is not recommended.

Bladder duplication and septation are also rare. In complete duplication, two functional bladders are found and are felt to possibly be the result of partial twining.[15] Various types of bladder duplication and septation have been described (Figure 63.3).[16] In 90% of bladder duplications, two separate urethras are found. In males duplication of the penis and in females duplication of the vagina and uterus are usually present. Management of this condition is aimed at maintaining normal lower urinary tract function and is tailored to the individual situation.

BLADDER TRAUMA IN CHILDREN

Given its location early in development, the bladder is an intra-abdominal organ until 4–5 years of age, at which point, with somatic growth, the bladder becomes a pelvic organ. Trauma to the bladder is a rare occurrence in children. It is usually associated with blunt trauma to a full bladder.[17] As in adults, the most common causes of blunt trauma to the bladder include motor vehicle accidents, falls, and sport injuries.[18] *In young children, the full bladder typically extends above the pelvic ring, allowing for bladder injuries to occur with blunt trauma to the abdomen without associated pelvic fracture.*[19] A classification of bladder injuries has been published by Sandler et al.[20] (Table 63.1).

FIGURE 63.1 Bladder hypoplasia in patient with chronic renal failure. Urine extravasation is noted after partial bladder emptying.

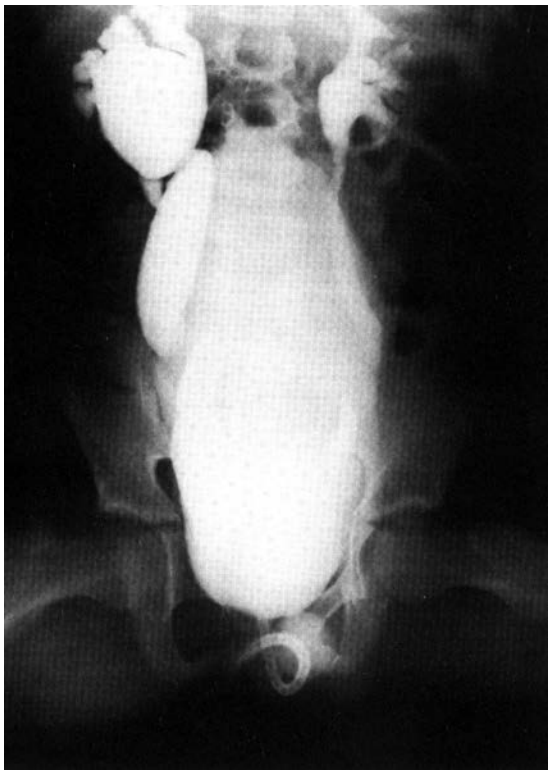

FIGURE 63.2 VCUG of a patient with megacystis–megaureter. Note the massive elongation and distention of the bladder with dilatation of the ureters associated with vesicoureteral reflux.

Bladder contusion involves damage to the bladder muscle and mucosa without disruption of the integrity of the bladder. In general, bladder contusion presents with gross hematuria. Imaging by either ultrasound or computed tomography (CT) scan will reveal a thickened, irregular bladder wall (Figure 63.4). Bladder contusion is present in one-third of all bladder injuries. The management of bladder contusion is usually expectant or with catheter drainage.

Rupture of the bladder can be classified as either intraperitoneal or extraperitoneal. The treatment is drastically different based on the above dichotomous findings and should be specific to the diagnosis and anatomy of the injury. Adequate radiological imaging is particularly important to differentiate between the two.

Intraperitoneal rupture is seen more commonly in children because of the anatomic location of the bladder. The mechanism of injury involves blunt trauma to the bladder, with an abrupt rise in intravesical pressure causing disruption of the bladder wall at the level of the dome, the weakest

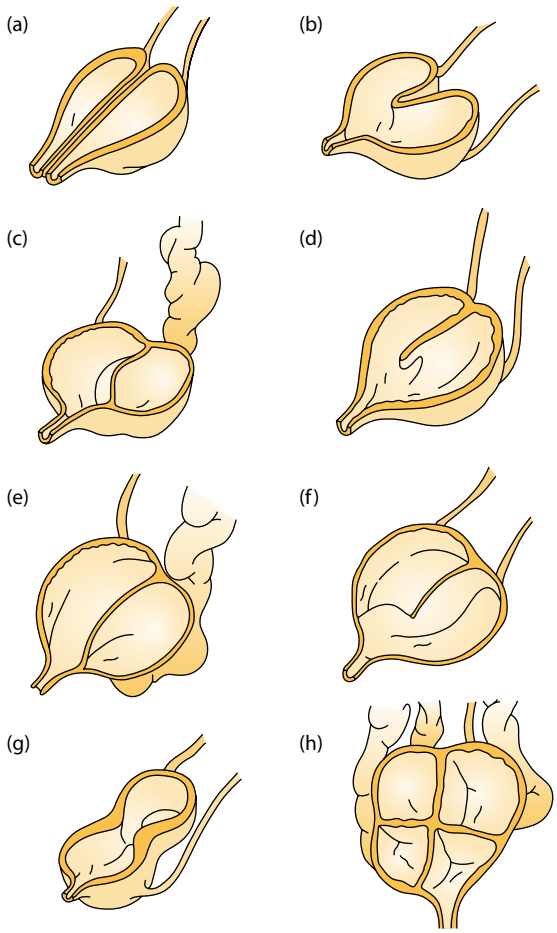

FIGURE 63.3 Various forms of bladder duplications and septations: (a) complete duplication, (b) incomplete duplication, (c) complete sagittal septum, (d) incomplete sagittal septum, (e) complete frontal septum, (f) incomplete frontal septum, (g) hourglass bladder, and (h) multiseptated bladder. (Reproduced with permission from Friedland GW, Devries PA, Nino-Murcia M, Cohen Rifkin MD. Congenital anomalies of the urachus and bladder. In Pollack HM, ed., *Clinical Urography* (Philadelphia: WB Saunders, 1990), 711–36.

portion of the bladder wall. In general, urine will extravasate into the peritoneal cavity due to disruption of the peritoneal lining of the bladder. Extravasation of the urine into the abdominal cavity will cause urinary ascites, peritoneal signs, and in the majority of cases, abnormal serum chemistries.[21] This helps to distinguish patients with extraperitoneal rupture who, in general, will display normal serum chemistries in the acute setting. Patients presenting early

TABLE 63.1 Categories of bladder trauma in children

Type 1 Bladder contusion
Type 2 Intraperitoneal rupture
Type 3 Interstitial bladder rupture
Type 4 Extraperitoneal rupture a. Simple b. Complex
Type 5 Combined bladder injury

FIGURE 63.4 CT scan of a patient showing contrast extravasation in the pelvis after extraperitoneal bladder rupture due to blunt trauma.

with intraperitoneal bladder rupture will display increased serum creatinine and potassium, whereas those presenting later will exhibit increased serum levels of blood urea nitrogen, creatinine, and potassium, and lower levels of serum sodium. Acidosis can also be occasionally observed.

Standard imaging techniques in patients suspected of having a bladder injury should include a CT scan of the abdomen and pelvis.[22] If this modality is not available, then a VCUG should be obtained.[23] The diagnosis of a bladder rupture can be difficult, and it must be accomplished with retrograde filling of the bladder through a urethral catheter. The contrast material should be instilled by gravity until the bladder is fully distended and post-drainage images, anteroposterior and oblique, must also be obtained. Retrograde bladder filling should be performed during CT scan imaging (CT cystogram) because simple administration of intravenous contrast may not allow full bladder distention.[24]

Imaging of intraperitoneal bladder rupture by either CT scan or cystography will demonstrate outlining of the large and small bowel loops by contrast material and evidence of dilute contrast extending from the pelvis up into the abdominal cavity, usually along the paracolic gutter (Figure 63.5). Unless the bladder is well filled and then emptied completely, evidence of contrast material extravasation may be easily overlooked. Careful instillation (by gravity) of contrast material during the cystogram and then emptying will reveal diffuse extravasation of the contrast in the abdominal cavity with extension on the posterior aspect in the supine patient. Forceful injection of contrast into the bladder is contraindicated because it may worsen the injury and potentially allow for bacterial seeding of the retroperitoneum and/or abdomen.

Extraperitoneal bladder rupture occurs in cases of blunt pelvic trauma, usually associated with a pelvic fracture. Various mechanisms of injury have been described, and the lower half of the bladder is usually involved.[25] Sandler et al. described four types of bladder injury due to blunt trauma and divided extraperitoneal rupture into simple

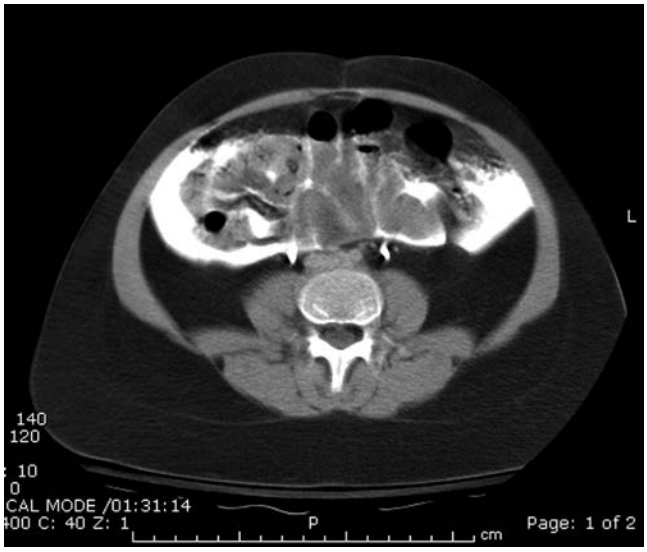

FIGURE 63.5 CT scan of patient with extravesical bladder rupture showing contrast extravasation extending into the abdomen along the paracolic gutters.

and complex.[20] This classification is based on the appearance of contrast extravasation during the cystogram. A simple extraperitoneal rupture will display contrast material extravasation limited to the pelvic extraperitoneal space. Complex extraperitoneal extravasation will show contrast material outlining the muscle groups in the thigh and diffusely throughout the pelvis. It may extend into the scrotum and perineum. Bony spicules, which can be the result of a fractured pelvis, may also contribute to the mechanism of injury. It is important to carefully assess the bladder and the surrounding structures for fragments of bone, which may contribute to further laceration of the bladder if left in place. CT scan is the best modality for detecting osseous fragments.

Management of bladder injuries is dependent on the type of injury diagnosed. In general, bladder contusion is either managed expectantly or treated with catheter drainage while gross hematuria is present. In general, the catheter can be removed once the urine has cleared and there is no evidence of passage of blood clots. Reimaging of the bladder is not necessary, although a pelvic ultrasound can be used to ascertain resolution of the intramural hematoma, rule out any extravesical collections, and assess the presence or absence of hydroureteronephrosis.

The standard management of intraperitoneal bladder rupture is open surgical exploration with repair of the bladder defect. This is usually carried out on an emergent or urgent basis, with concomitant exploration and irrigation of the peritoneal cavity. Once the bladder injury has been repaired, bladder drainage is accomplished by either suprapubic tube or a urethral catheter.[26] Urethral catheters appear to be as effective in draining the bladder as suprapubic catheters, and will usually ensure a shorter period of diversion.[27] Prior to removal of the drainage catheter, a cystogram should be carried out to ensure that the integrity of the bladder has been restored.

Simple extraperitoneal bladder ruptures can be treated nonoperatively with urethral catheter drainage for 7–10 days. However, if a patient has experienced more complicated injuries involving the pelvis with the presence of bony spicules or fragments within the bladder, then surgical exploration can be considered to remove the fragments of bone and carry out bladder repair and drainage. Again, follow-up cystogram is warranted to ensure that bladder healing has occurred and that there is no evidence of persistent extravasation. There are, in general, no long-term consequences of bladder injury or rupture in simple cases.[28] However, in the more complicated cases involving pelvic fracture and multiorgan injuries, and in those with evidence of a urethral disruption, the complication rate rises significantly.

BLADDER DIVERTICULA

F. Douglas Stephens published the first series of bladder diverticula in children in 1960.[29] The advent of cystography had allowed the evaluation of children who presented with urinary tract infections. A number of these patients were found to have smooth bladders and what was then described as saccules at the ureterovesical junction. Saccules had been previously reported in trabeculated bladders secondary to bladder outlet obstruction in adults. Douglas Stephens and subsequently John Hutch proposed that there would be two possible etiologies to bladder saccules or diverticula: (1) those secondary to bladder outlet obstruction and (2) those that may be congenital and seen in association with a smooth bladder wall.[30] Classification of bladder diverticula in children can therefore be based on their etiology: (1) those associated with bladder outlet obstruction, including posterior urethral valves, urethral strictures, large prolapsing ureterocele, and neurogenic dysfunction; (2) those occurring after bladder surgery, specifically after ureteral reimplantation when the hiatus is not reinforced, causing iatrogenic weakening of the paraureteral detrusor layer; (3) those associated with specific syndromes, more frequently prune belly, Menkes, Williams, and Ehlers–Danlos syndromes; and (4) those felt to be primary, congenital, or idiopathic diverticula with or without vesicoureteral reflux.[31,32] Bladder diverticula in children may be single or multiple. They may be found in up to 1.7% of children evaluated by cystogram.[31]

A bladder diverticulum represents a herniation of the bladder mucosa between fibers of the detrusor muscle, resulting in outpouching into the perivesical space. The exact etiology of congenital bladder diverticula is not known but is thought to represent an intrinsic weakness in the muscle wall of the bladder. They are most commonly seen adjacent to the ureteral orifice, as described by John Hutch in 1961.[30] The discussion in this chapter is limited to congenital bladder diverticula and diverticula associated with various congenital syndromes. Not discussed are diverticula associated with bladder outlet obstruction and neurogenic bladder. Congenital syndromes in which bladder diverticula are seen include Menkes kinky hair syndrome (a connective tissue disorder characterized by increases in tissue copper and metallothionine contents);[33] Ehlers–Danlos syndrome (a syndrome characterized by defective collagen synthesis, resulting in joint hypermobility, skin extensibility, and tissue fragility), which is usually

inherited as an autosomal dominant condition;[34] cutis laxa (a syndrome characterized by decreased or absent elastic tissue); and finally, Williams syndrome (a disorder characterized by mental retardation, growth abnormalities, facial anomalies, and aortic stenosis).[35] Williams syndrome is associated with gene deletion on chromosome 7q, a region in which the *ELN* gene is located (a gene coding for elastin synthesis).[36] Patients with Williams syndrome have also been found to have a higher rate of renal abnormalities, suggesting the need for screening of the upper urinary tract by ultrasound.[37]

Bladder diverticula associated with chromosomal abnormalities are usually multiple and may cause bladder dysfunction. The patient has the ability to store urine but is unable to completely empty the bladder. Urinary stasis, with resultant urinary tract infections, may be the only manifestation of the bladder diverticula (Figure 63.6). Frequent, complete bladder emptying, potentially using clean intermittent catheterization, will help prevent stasis and possibly infection. *Surgical excision of bladder diverticula in patients with chromosomal abnormalities must be considered with caution, as the diverticula are multiple and may recur once surgical excision has been carried out.*

Congenital bladder diverticula are discovered, in general, in the course of the evaluation for urinary tract infection when a cystogram is carried out. Equal male-to-female distribution is noted. Bladder diverticula are usually asymptomatic, but bladder obstruction or ureterovesical junction obstruction symptoms have been reported.[38,39] Bladder outlet obstruction may be caused by an enlarging bladder diverticulum that extends inferiorly to compress the bladder neck or proximal urethra. Also, and depending on the size and location of the diverticulum, the ureteral hiatus may be incorporated in the diverticulum (Figure 63.7).

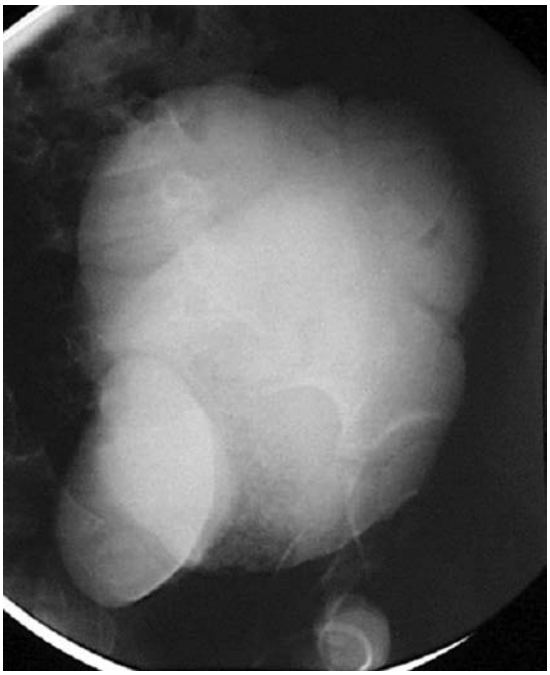

FIGURE 63.6 Cystogram of a 6-year-old patient who presents with recurrent urinary tract infection and incontinence. A large bladder diverticulum is seen on the right side of the bladder.

FIGURE 63.7 Cystogram view demonstrating a bladder diverticulum associated with vesicoureteral reflux. Note the contrast in the ureter, which inserts into the diverticulum.

Periureteral diverticula can, in effect, distort the normal ureterovesical junction and cause an abnormal intramural tunnel, thus altering the normal antireflux mechanism. As a result, vesicoureteral reflux may then occur.[40] Vesicoureteral reflux is associated with bladder diverticula but may not always be apparent on a VCUG and has been reported with a wide variability.[41] In addition to reflux, bladder diverticula may also be associated with distal ureteral obstruction in up to 5% of cases.[42]

Although bladder diverticula are often diagnosed incidentally during radiological evaluation for a urinary tract infection, the relationship between urinary tract infection and bladder diverticula remains unclear. It has been postulated that large bladder diverticula may predispose to urinary stasis, which, in turn, will provide a nidus for bacterial growth.[43,44]

Urinary tract infections in children with abnormal voiding patterns warrant close evaluation by ultrasound of the bladder and kidneys and a VCUG. These children may be found to have detrusor sphincter dyssynergia, hyperreflexia, or hypertonia. Specifically, patients with Hinman–Allen syndrome (nonneurogenic neurogenic bladder) have been reported to have associated periureteral diverticula.[45] A VCUG is the usual diagnostic modality, which allows bladder diverticula to be found; however, they can also be noted on bladder ultrasound and CT scan of the pelvis. Intravenous urogram will usually not allow the detection of bladder diverticula because the bladder will overlie the diverticulum and the diverticulum may be filled with dilute contrast material. Larger diverticula can also be confused with other bladder lesions, such as urachal cysts, bladder ears seen in very young children, bladder herniation, ectopic ureteral insertion at the bladder neck, bladder duplication, everting ureteroceles, and ureteral stump resulting from excision of the upper part of the ureter and kidney (Table 63.2).

TABLE 63.2 Differential diagnosis of bladder outpouching in the pediatric age group

- Urachal cyst (dome of bladder)
- Bladder ears (seen in young babies)
- Bladder herniation (seen in large inguinal hernias)
- Ectopic ureteral insertion (usually at or around the bladder neck)
- Bladder duplication
- Everting ureterocele
- Refluxing ureteral stump

The relationship between bladder diverticula and voiding dysfunction has not been thoroughly clarified. Very few studies have used urodynamic evaluation to assess bladder physiology in the face of bladder diverticulum. Interestingly enough, Douglas Stephens, as early as 1960, attempted to evaluate bladder pressures in 4 patients of his series of 23 patients with bladder diverticula.[29] The main issue shrouding the urodynamic assessment of bladders associated with bladder diverticula is the fact that pressure recordings are difficult to interpret given the compliant nature of the bladder diverticulum. Thus, cystometrogram may be notoriously unreliable. However, detrusor sphincter dyssynergia, if present, may be diagnosed by doing a videourodynamic study.

The upper urinary tract may also be abnormal in the face of a bladder diverticulum. As noted, there is a variable rate of vesicoureteral reflux associated with bladder diverticulum. In addition to vesicoureteral reflux, 16%–30% of patients with bladder diverticula have been reported to have renal abnormalities in early studies, although this is likely to be a gross overestimate based on modern imaging.[46,47] These abnormalities range from focal dysplasia to multicystic dysplastic kidney. Renal lesions have also been reported in patients with vesicoureteral reflux and a history of febrile urinary tract infection. Upper tract dilatation may also be observed in cases where the bladder diverticulum causes obstruction by extrinsic compression of the distal ureter.[38] An early report from France documented 7 of 43 cases of patients with bladder diverticula having evidence of renal dysplasia or multicystic dysplastic findings.[46] In a later study by Tokunaka et al. out of Japan, 17 patients were evaluated, 13 of whom showed dilatation of the upper collecting system associated with renal scarring, and 4 had small nonfunctioning kidneys.[47] The authors correlated the severity of the renal abnormalities with the position of the ureteral orifice in relationship to the diverticulum and postulated that abnormalities in ureteral bud formation may have impacted normal nephrogenesis. When the ureter inserted directly into the diverticulum, the likelihood of cystic dysplastic changes in the kidney increased. In light of the fact that a significant number of patients with bladder diverticula have upper tract changes, further functional evaluation of the kidney may be warranted in the form of a dimercaptosuccinic acid (DMSA) renal scan. On the other hand, most of these patients likely presented with symptoms related to their renal pathology, and were subsequently found to have bladder diverticula, so the overall likelihood of renal anomalies associated with diverticula is much smaller.

The management of patients with congenital bladder diverticula depends on the presentation and symptoms. As noted, most patients present with urinary tract infection. Evaluation and treatment of any bladder dysfunction should be considered prior to any attempts to treat the diverticulum surgically. It should be noted that some children with small bladder diverticula and lower grades of vesicoureteral reflux may outgrow the reflux and have the diverticula disappear.[41] *The indication for surgical treatment of bladder diverticula is dictated by the presence of persistent high-grade vesicoureteral reflux and recurrent urinary tract infections, or documented obstruction of either the distal ureter or the bladder neck*. In cases of functional bladder outlet obstruction due to a very large diverticulum extending underneath the bladder neck, excision of the diverticulum is recommended. In patients with recurrent urinary tract infection and persistent vesicoureteral reflux, diverticulectomy is recommended and should be accompanied by reimplantation of the ureter.

The surgical approach can be either intravesical or extravesical. The key surgical principle is to reinforce the muscular hiatus of the bladder to prevent reformation of the bladder diverticulum. Should the upper tract evaluation reveal a nonfunctioning kidney, consideration should be given to nephroureterectomy with diverticulectomy. Extravesical approaches and laparoscopic or robotic techniques can be used in these cases.[48–50]

URACHAL ANOMALIES

The urachus is an embryologic remnant derived from both the allantois and a part of the bladder.[51] Early in fetal development, the bladder descends toward the pelvis, retaining its attachment to the umbilicus through the urachus. The urachus has a lumen early in gestation that spontaneously closes, but may remain patent in cases of bladder outlet obstruction, such as posterior urethral valves.[2] However, in humans the urachus appears to close very early in gestation and rarely remains patent. Closure of the urachus is thought to occur between the fourth and fifth month of gestation by progressive accumulation of desquamated epithelium within the lumen. Anatomically, the urachus is identified between the umbilicus and the dome of the bladder. It is 3–10 cm in length and 8–10 mm in diameter. It is surrounded by the umbilical sheath, which extends on either side to the umbilical arteries and down to the bladder dome. The urachus is composed of three histological layers, and a central lumen is usually hard to identify. Congenital anomalies of the urachus result from abnormal involution of the urachus. They are rare and usually are asymptomatic until adulthood. Typical presenting symptoms in children are periumbilical discharge (42%), umbilical mass (30%), abdominal or periumbilical pain (22%), and rarely dysuria (2%).[52] In a series of 26 patients, McCollum et al. 11 (42%) presented with infection, 7 (21%) with clear drainage from the umbilicus, 3 (12%) with polypoid granulation of the umbilicus, 3 (12%) with pain, 1 (4%) with recurrent urinary tract infections, and 1 (4%) with an asymptomatic sinus.[53]

Urachal anomalies can be divided into urachal sinus, urachal cyst, patent urachus, and vesicourachal diverticulum (Figure 63.8). They are isolated defects and are not associated with specific syndromes or conditions, with the exception of bladder outlet obstruction (rare) or prune

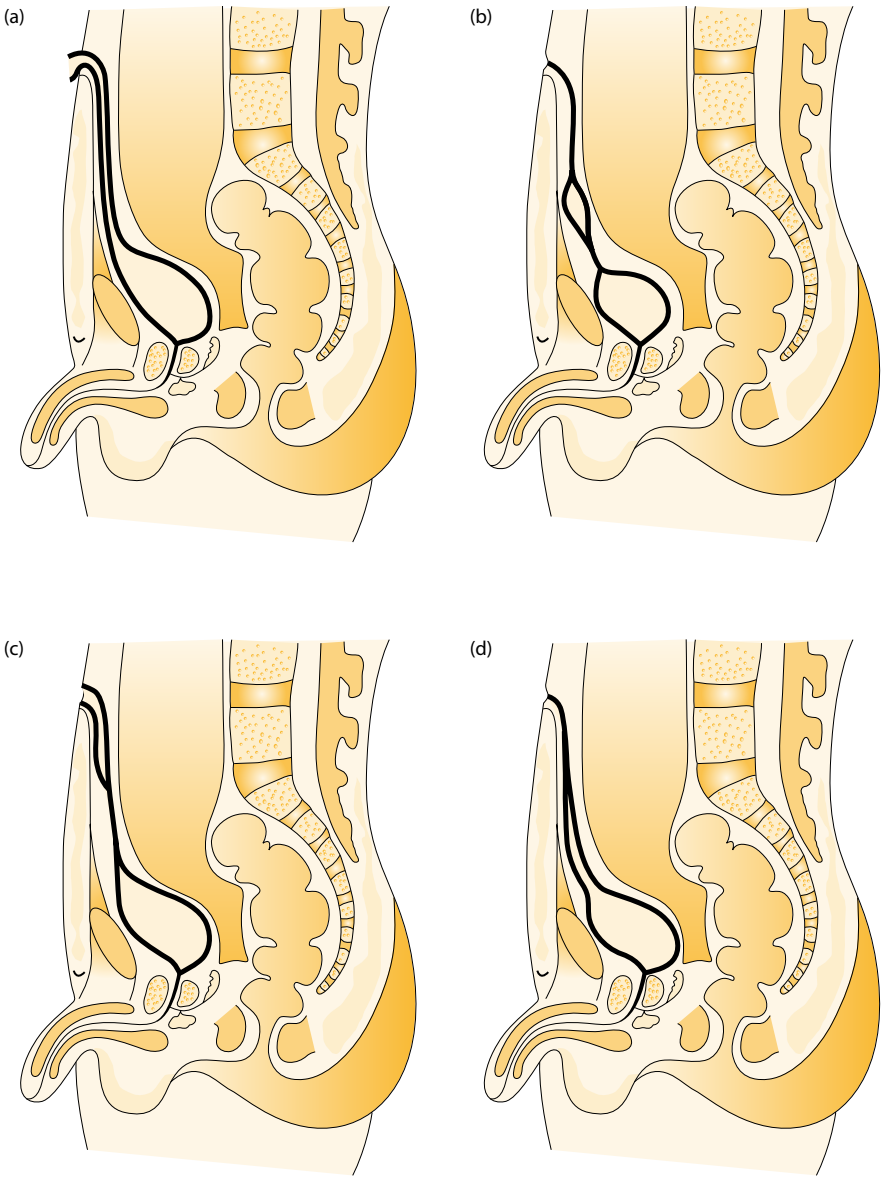

FIGURE 63.8 Congenital urachal anomalies: (a) patent urachus, (b) urachal cyst, (c) urachal sinus, and (d) vesicourachal diverticulum. (From Schnyder PA, Candardjis G. *AJR Am J Roentgenol* 1981;137(5):1063–5. Copyright American Roentgen Ray Society.)

belly syndrome.[54] Diagnosis of urachal anomalies is made either by careful physical examination or by radiographic evaluation. Children with a draining umbilicus should undergo an injection of the draining sinus with contrast.[55] Alternatively, a cystogram may reveal a patent urachus. A child presenting with a periumbilical mass should be evaluated with ultrasonography or, alternatively, with a CT scan.[56]

A urachal sinus occurs when the lumen of the urachus fails to completely obliterate. Children will present with intermittent or persistent drainage from the umbilicus. Occasionally, granulation tissue can be seen at the site of the lumen. A urachal sinus can become infected and inflamed, causing lower abdominal pain with fever. Very occasionally, patients will present with lower abdominal pain occurring at the end of voiding. This is due to tension on the inflamed urachal remnant. Dimpling of the umbilicus may also be reported. A sinogram is the diagnostic test of choice in this situation. Complete surgical excision of the sinus tract and resection of the omphalomesenteric duct remnant should be carried out. If an inflammatory process has been present, injury to the intraperitoneal structures is more likely, as adhesions may have formed around the urachal remnant.[57]

Urachal cysts are quite rare clinically, but reported in up to 1 in 5000 in autopsy series.[58] Urachal cysts are usually found in the distal third of the urachus. Urachal cysts will present during late childhood and early adulthood either as an asymptomatic suprapubic mass or with suprapubic pain and/or irritative voiding symptoms. Bacterial colonization and infection (usually caused by *Staphylococcus aureus*) can occur.[59,60] The infection is usually confined to the space of Retzius, but rupture of the infected cyst may cause peritoneal contamination and intraperitoneal involvement.[61,62] Severe sepsis associated with a urachal abscess has also been reported.[63]

The diagnosis of a urachal cyst is achieved by either ultrasound or CT scan. Ultrasonography allows for accurate delineation of the cystic structure and its position relative to the bladder and the peritoneum.[56] CT scan may be helpful in cases of infected urachal cyst to determine the extent of the cyst and inflammatory process, which may be quite large and involve adjacent structures, such as bowel (Figure 63.9).[64] Bladder involvement can also occur and be better defined by a VCUG or cystoscopy.

Treatment of urachal cysts is usually tailored to the presentation. Small asymptomatic cysts may be observed. Symptomatic cysts may be excised by either open or laparoscopic and robotic techniques.[65,66] Infected cysts should be treated with a staged approach: first, incision and drainage with antibiotic coverage, followed by surgical excision once the inflammatory process has subsided, as documented by follow-up imaging.[67]

Patent urachus is a rare anomaly due to failure of obliteration of the lumen of the urachus. Such a situation may be seen in prune belly syndrome and rarely in posterior urethral valves. A patent urachus may be identified incidentally in the newborn when clear drainage is noted from the umbilicus. Symptoms can include intermittent drainage, and periumbilical swelling in association with an umbilical hernia. Granulation tissue may be seen and can mimic other umbilical lesions, such as a healing umbilical stump, a patent vitelline or omphalomesenteric duct, or an infected umbilical vessel. The diagnosis of patent urachus can be made by collecting fluid and analyzing its creatinine level. Injection of the lumen with contrast or a voiding cystogram will confirm the diagnosis. The fistulous tract should be seen extending from the dome of the bladder to the umbilicus (Figure 63.10).

Management of a patent urachus can be expectant, as a number of children will experience spontaneous closure in the first month of life.[68] In children with bladder outlet obstruction, treatment of the obstructive process will, in general, allow for spontaneous closure. Excision of the urachal tract is reserved for those patients in whom drainage persists. Surgical removal of a bladder cuff is usually recommended to ensure that all remnants of the urachus are removed.

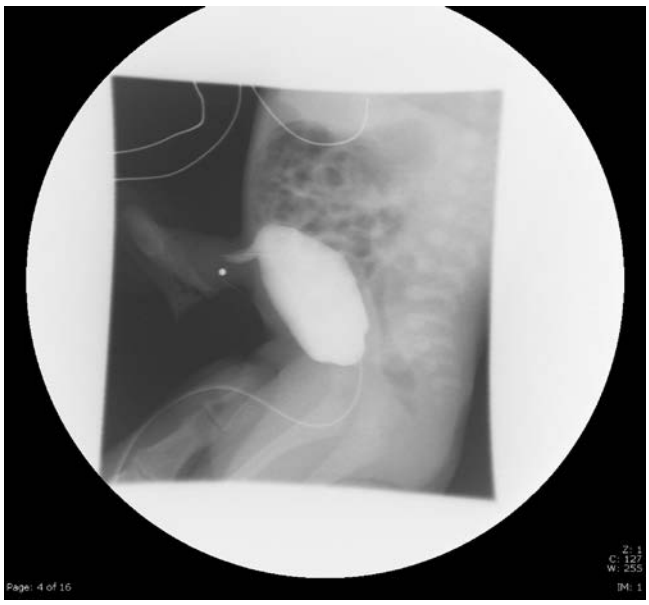

FIGURE 63.10 Patent urachus in a 3-month-old boy who presented with persistent clear drainage from his umbilicus. Note the small lead ball placed at the umbilical site of drainage to help with three-dimensional localization. Contrast extends from the dome of the bladder to the base of the umbilicus, with the feeding tube in the urachus.

FIGURE 63.9 CT scan image of a patient with a pyourachus. Note the large inhomogeneous area anterior to the bladder corresponding to the abscessed urachal cyst. The patient underwent percutaneous drainage and subsequent excision of the urachal cyst.

Vesicourachal diverticula are usually found incidentally on a VCUG. Failure of closure of the lumen at the level of the bladder dome allows for the formation of a fusiform outpouching (Figure 63.8). In general, these lesions are of little or no clinical significance. Surgical excision is required if the diverticulum does not drain well or is symptomatic.

Urachal anomalies are known to be associated with malignant degeneration in the adult population, usually in the form of urachal carcinoma (adenocarcinoma). Other forms of malignancy have also been reported, such as transitional cell carcinoma, neuroblastoma, rhabdomyosarcoma, teratoma, and yolk cell sarcoma.[69,70] While malignant degeneration is rare and accounts for 0.34% of all bladder cancers, management of urachal anomalies may be skewed toward surgical excision. Observation in children is certainly reasonable using yearly ultrasound as a monitoring technique. However, parents and patients should be educated as to the malignant potential of these lesions.

INFLAMMATORY CONDITIONS OF THE BLADDER IN CHILDREN

Inflammatory conditions of the bladder include eosinophilic cystitis and interstitial cystitis (IC). Fewer than 25 cases of eosinophilic cystitis have been reported in children.[71] Eosinophilic cystitis may be diffuse or localized

and present as an intravesical mass. Symptomatology will usually be irritative voiding symptoms with frequency or urgency, suprapubic pain, and hematuria. Ultrasound imaging of the bladder may reveal diffuse thickening of the bladder, and the diagnosis will be made by cystoscopy and biopsy of the lesion. The disorder is felt to be caused by an antigenic stimulus (infection or foreign body) that triggers an immunoglobulin E–mediated eosinophilic invasion of the bladder wall. Degranulation of the eosinophils then promotes release of inflammatory mediators. The process is felt to be self-limited with little or no consequences on the lower urinary tract.[72] Various therapeutic modalities have been reported to alleviate symptoms. These modalities include antibiotics, antihistamines, corticosteroids, cyclosporine A, surgical resection of the lesion, and even partial cystectomy.[73] The condition is occasionally seen in association with chronic granulomatous disease.[74]

Myofibroblastic tumor of the bladder is another rare inflammatory condition seen in children. Symptoms are similar to those of eosinophilic cystitis. A distinct mass is seen on ultrasound, and histologically these lesions are characterized by spindle cells with myofibroblastic and fibroblastic proliferation associated with a prominent inflammatory process.[71] Etiology of this condition has not been elucidated. The lesions may be fairly aggressive and may reoccur. Transurethral resection may be curative, but large tumors may require more extensive (open) resection. These tumors are benign but should be differentiated from sarcomas or lymphomas. Immunohistochemical staining is the best way to evaluate these lesions.[73] As noted previously, eosinophilic cystitis may also present as a discrete mass, but histologically the lesion appears less invasive than myofibroblastic tumors.

IC has been reported in children and in adolescents.[75,76] However, its incidence is hard to ascertain, as it is a difficult diagnosis to make and thus may go underreported. Held et al. note that adult women with IC are 10–12 times more likely to report childhood bladder problems than a group of matched controls.[77] In the face of irritative voiding symptoms associated with painful bladder, cystoscopic and histological findings are needed to make the diagnosis of IC in children and adolescents. In a relatively small cohort of patients, Close et al. documented IC in 16 children under 16 years old.[76] All were treated by hydrodistention, and half of them responded, while the rest required further therapy. Bladder compliance was reduced in only three cases.

IC should be considered a possible diagnosis in children with severe irritative symptoms associated with painful bladder who do not respond to first-line therapy. However, the diagnosis of IC may be elusive.[78]

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CHAPTER 64

Posterior Urethral Valves

Stephen A. Zderic and Douglas A. Canning

BACKGROUND

Hugh Hampton Young initially described posterior urethral valves and proposed the current classification scheme.[1] Dewan et al. argued for an alternative to Young's system and proposed the term *congenital posterior urethral membrane*.[2] Regardless of the classification, it is clear that this anomaly presents with great variability.[3] *Posterior urethral valves occur in 1 in 5000 live births, which would mean that some 400 to 500 new cases occur in the United States every year.* While this might seem to be a small number of cases, one must consider that within this annual patient cohort, approximately 150 will develop end-stage renal disease (ESRD) and require either dialysis or transplantation within their first 18 years. Given today's advances in dialysis and transplantation, and life expectancies that will approach 70–80 years, this small number of patients places a substantial financial burden on the healthcare system. Clearly anything that can be done to lower the incidence of ESRD in this population will have a substantial societal impact, in addition to a profound effect on the lifestyle of the boy and his family.

EMBRYOLOGY AND CLASSIFICATION

In Young's original classification, *type 1 posterior urethral valves begin as leaflets that originate at the distal aspect of the verumontanum and then fan out to fuse in the midline just proximal to the external striated sphincter. Type 1 valves are a hypertrophied variant of the inferior urethral crest, which is formed by the insertion of the distal ends of the Wolffian ducts into the anterolateral walls of the cloaca*.[4] Stephens believed that the remnants of the normal urethral crest are visible as nonobstructing ridges that sweep inward from the lateral walls of the prostatic urethra and converge in the midline at the verumontanum (Figure 64.1). Cranial to this fusion at the veru, the Wolffian ducts and associated ureteral buds are absorbed into the bladder neck and trigone. If, however, the Wolffian ducts should insert into the anterior wall of the cloaca, these folds would become more prominent with a propensity to fuse in the midline. Depending on the degree to which this occurs, the valve leaflets will then become obstructive in nature. Type 1 valves account for 90%–95% of all cases. *Type 2 valves in Young's original classification are not obstructing, and reflect mucosal folds extending from the verumontanum superiorly to the bladder neck.*

Type 3 valves represent a circumferential annulus that resembles a stricture. These account for 5%–10% of all cases of posterior urethral valves. Their embryologic origin is different and probably arises from a persisting urogenital membrane.[4] The urogenital membrane is the anterior portion of the cloacal membrane that the urorectal septum divides.

The exact embryologic origins of posterior urethral valves remain unclear, and await further study, with modern molecular techniques being applied to fetal and neonatal postmortem specimens.[5] While there are numerous knockout mice described with abnormalities of ureteral budding, none develop posterior urethral valves. Thus far, the only models of posterior urethral valves involve the surgical creation of partial or complete fetal bladder outlet obstruction in several species.

SPECTRUM AND CONSEQUENCES OF POSTERIOR URETHRAL VALVES

Mild cases of posterior urethral valves may remain asymptomatic until adolescence or even adulthood. Severe cases usually present in utero with abnormal fetal sonography. Alternatively, they may present in the neonatal unit with a palpable bladder and urinary retention. In the most severe cases, as shown in Figure 64.1, the bladder outlet obstruction from the valve results in severe hydroureteronephrosis and cystic dysplasia within the kidney. In these boys, pulmonary hypoplasia is the cause of death in the neonatal period. However, the primary pathophysiology begins with the onset of partial bladder outlet obstruction.

PATHOPHYSIOLOGY OF BLADDER OUTLET OBSTRUCTION

The varied spectrum of outcomes noted in boys born with valves may represent differences among patients in the degree of obstruction, the timing of the obstruction, and underlying genotypic risk factors. To better understand these diverse outcomes, a brief discussion of the pathophysiology of bladder outlet obstruction is important. In

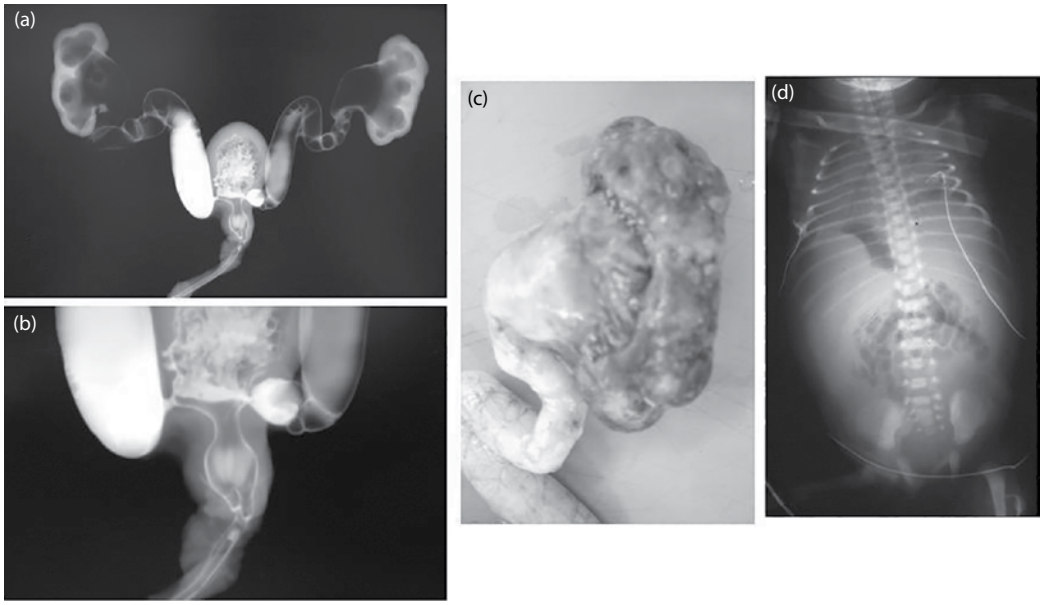

FIGURE 64.1 The consequences of severe type 1 posterior urethral valves. (a) Severe bladder wall thickening was associated with bilateral reflux in this postmortem retrograde study performed ex vivo. (b) The hallmark of type 1 valves is the origin of the cusps at the verumontanum, which fan out laterally and fuse in the midline. (c) Associated with this is severe cystic dysplasia. (d) Because of the oligohydramnios in utero, severe pulmonary hypoplasia developed in the neonatal period that was the cause of death. (Panels a–c courtesy of Dale Huff, MD, and Christopher Austin, MD.)

a simplified scheme, partial bladder outlet obstruction begins with the onset of bladder wall hypertrophy that enables the bladder to adapt to its new workload. During this compensated phase, the bladder is capable of generating a high voiding pressure, and may empty nearly completely. Over time, however, these compensatory mechanisms fail to keep pace with the demands, and the volume of the postvoid residuals begins to increase. The rising storage pressures within the bladder are transmitted to the renal pelvis, calyces, and ultimately, the glomerulus, resulting in renal damage. The pathophysiology of this process is complex, and incompletely understood. It is, however, clinically important given that long-term bladder dysfunction may plague these patients in their daily lives despite successful valve ablation.

Effects on Bladder Function

The impact of partial outlet obstruction on subsequent bladder function has been the subject of ample investigation. A review of the literature reveals myriad studies using human tissues taken at the time of surgery, as well as a large number of fetal and adult animal models. In this brief overview, we hope to summarize the steps that lead to bladder dysfunction in the face of partial outlet obstruction. There is evidence to support the following tenets: *the presence of partial outlet obstruction leads to an increase in smooth muscle size (hypertrophy) and a hyperplasia of interstitial cells (fibroblasts and myofibroblasts) that increase their deposition of extracellular matrix. The pathophysiological changes in the bladder wall lead to an alteration in blood flow to the detrusor that ultimately results in ischemia, a shift to anaerobic metabolism, and damage to the nerves within the bladder wall.*

If one characterizes disorders of voiding into failures of bladder storage or bladder emptying, one can understand how partial bladder outlet obstruction interrupts this cycle. Mitchell summarized this concept nicely in a diagram (Figure 64.2) that illustrates that mild hypertrophy follows outlet obstruction, which results in higher voiding pressures that initially preserve near-complete bladder emptying. However, as this filling and emptying cycle repeats, further remodeling of the bladder wall occurs, and gradually the postvoid residual begins to increase. In the developing fetus with posterior urethral valves, the rise in urine output that accompanies normal growth and development further stresses this system. *Ultimately, the*

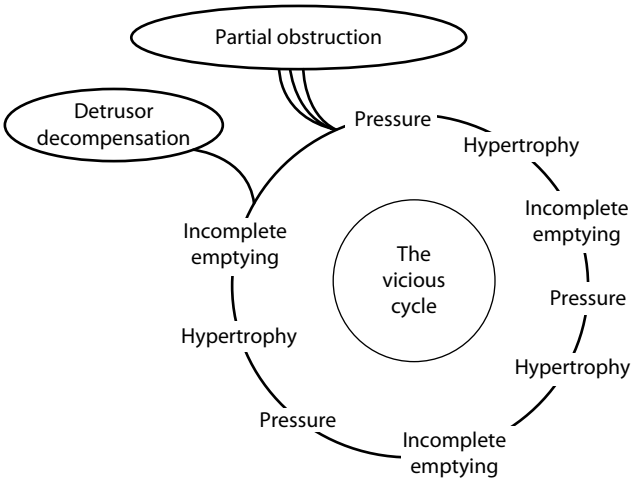

FIGURE 64.2 Mitchell's schematic concept of how partial outlet obstruction affects the bladder cycle and over time alters the bladder.

bladder's ability to adapt cannot keep pace with the functional demands, and the detrusor decompensates. In this setting, the bladder continues to produce elevated voiding pressures, but it does so inefficiently, at the expense of an elevated resting pressure before voiding, and a markedly increased postvoid residual.

Does the bladder have a functional reserve upon which additional demands may be imposed without penalty? Sullivan and Yalla[6] offered evidence in favor of the detrusor functional reserve, which they defined as the peak *isometric* pressure (measured by balloon occlusion of the outlet) minus the peak *voiding* pressure (measured with the balloon deflated). With mild obstruction and a minimal postvoid residual, this number was always in excess of 40 cm H_2O. However, as the detrusor reserve dropped, the postvoid residual began to rise. As a result of this rise in the residual urine, the patient's bladder spends more time "living on the right side" of the cystometry curve, where the storage pressures will be higher. These studies were done in adults and, for technical reasons, have not been replicated in the fetus, but it is logical to assume that a similar concept would apply in the fetal setting.

Experimental models of fetal partial bladder outlet obstruction have provided some insight into this pathophysiology.[7] Cystometry following partial outlet obstruction in the fetal sheep revealed a spectrum of curves similar to that noted in other models. Kirsch et al.[8] noted a remarkable increase in bladder compliance ($\Delta V/\Delta P$) following partial outlet obstruction. In fact, the more compliant bladders were associated with upper tract dilatation. Because these cystometrograms were performed in the operating room, the ureters could be occluded, which means that these measures were a true reflection of isolated bladder compliance. These data would suggest that as the bladder underwent decompensation, the upper urinary tract was placed at risk.[9] Using the fetal sheep model of partial outlet obstruction, several groups have described a large distended bladder with poor contractile performance of selected muscle strips in vitro.[10,11] Similar findings were noted in a rabbit model of fetal bladder outlet obstruction by Rohrmann et al.,[12,13] who performed in vitro cystometry and noted an increased bladder capacity with low intravesical pressures. The common theme across all these models was the marked deposition of extracellular matrix elements between the muscle bundles, which is very similar to what is described in specimens from patients with posterior urethral valves.[14]

Basic research has succeeded in answering some of the following fundamental questions about the bladder's response to outlet obstruction.

What are the molecular pathways that account for the less efficient bladder function seen following outlet obstruction? Understanding these steps is critical if one tries to prevent damage to the bladder during the course of gestation using pharmacologic intervention. This approach is important in the fetus because surgical intervention for valves in the fetus has been shown to carry as high as a 50% fetal mortality rate.[15] In order to realize this goal, we need to understand the molecular pathways that lead to bladder dysfunction in the face of partial outlet obstruction. A simplified scheme of this complex pathophysiology is suggested in Figure 64.3.

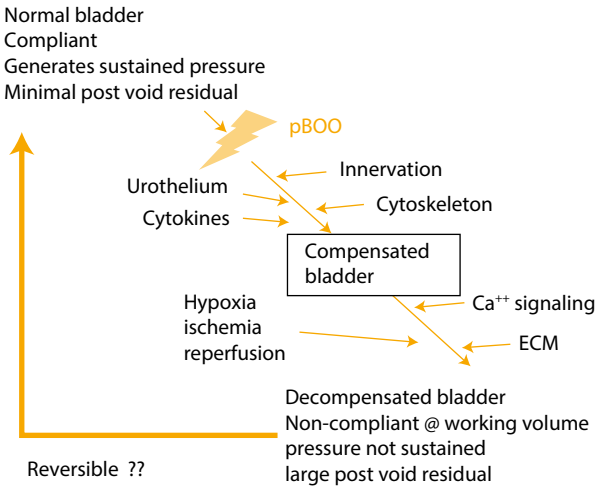

FIGURE 64.3 Schematic representation of the proposed sequence of events that result when a bladder is subjected to partial outlet obstruction. Early changes take place that allow for a bladder to *develop compensated function and generate higher pressures with minimal increases in postvoid residuals.* However, over a prolonged period of time, *additional changes take place and the postvoid residuals begin to rise, reaching the stage termed decompensated.* Although there is experimental evidence to support a role for each of these proposed contributing factors, the exact sequence of these events remains poorly understood. (Concept and figure developed by Bagli DJ, Wilcoxon DT, Kogan B, Zderic SA.)

Does the bladder respond to the rise in intraluminal pressure or to stretch? Numerous studies suggest that the progressive stretch resulting from outlet obstruction is the key factor mediating these molecular changes. Park et al. demonstrated this concept in a rat model of complete outlet obstruction in which the upper half of the bladder was constrained within a tube that allowed it to "sense" pressure, but prevented distention.[16] Park noted changes in cyclooxygenase 2 (COX-2) expression only in those bladder segments that were able to stretch, and not in those segments in which the restricting collar inhibited stretch. Furthermore, these changes in COX-2 expression were recapitulated in cultured cells subjected to mechanical deformation.[17] With an in vitro rat whole bladder model subjected to distention, Bagli and coworkers showed an increase in mRNA expression for collagen types I and III, as well as an increase in integrin expression.[18] Using human bladder smooth muscle cells subjected to mechanical stretch in vitro, Adam et al. showed changes in expression of some 20 genes (out of almost 12,000 analyzed) using microarray technology.[19]

Is Partial Outlet Obstruction Associated with Bladder Wall Hypoxia?

Hossler and Monson demonstrated using vascular resin casting, followed by tissue digestion and microscopy, that a rich capillary plexus exists within the bladder wall (it is especially prominent within the lamina propria region) (Figure 64.4).[20] Thus, it is not surprising that with overdistention, the perfusion of the detrusor is diminished, resulting in hypoxia. Using a porcine model of partial

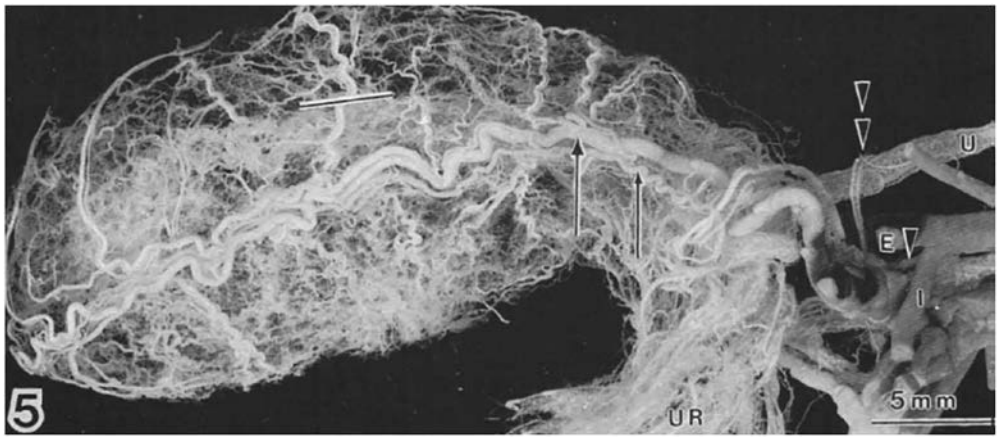

FIGURE 64.4 This resin cast of the rabbit urinary bladder shows a rich vascular architecture within the bladder wall that can be compressed to alter resistance with overdistention. (From Hossler FE, Monson FC. *Anat Rec* 1995;243(4):438–48. Reproduced with permission.)

outlet obstruction, Greenland and Brading demonstrated a marked drop in wall oxygen tension that was more pronounced with voiding.[21] Similar findings have been noted by other groups.[22] Levin and coworkers have observed increases in the expression of hypoxia-inducible factor (HIF), a transcription factor activated in the presence of lowered oxygen tension.[23] Stephany et al., using an acute preparation of bladder distention at constant pressures, showed an increase in HIF gene expression.[24] Azadzoi et al. documented alterations in bladder wall perfusion in atherosclerotic rabbits, and even in the absence of outlet obstruction, bladder wall hypoxia was associated with a marked deposition of extracellular matrix.[25] This is significant, as there is evidence to connect hypoxia with the profibrotic cytokine connective tissue growth factor (*ctgf*),[26] in part because the promoter site for *ctgf* contains a consensus binding sequence for HIF.[27] Growing evidence suggests that much of the hypoxic damage is the result of free radical toxicity,[28] and that the reperfusion phase is even more damaging than the hypoxia.[29] This hypoxic injury is especially damaging to the neural structures within the bladder wall and is substantiated with in vivo studies using the fetal sheep model of partial outlet obstruction.[10,11]

Which components of the bladder wall are affected by outlet obstruction, and where does the DNA synthesis take place? Following outlet obstruction, several changes in bladder morphology have been documented. There is an increase in smooth muscle size[30] (i.e., hypertrophy), and there is a prominent deposition of extracellular matrix components within the bladder wall. This has been shown in both human fetal specimens[14] and numerous fetal models of partial outlet obstruction.[8] It has been known for some time that bladder wall DNA synthesis takes place following outlet obstruction. Monson et al. showed this to take place within the lamina propia using pulsed tritiated thymidine and autoradiography,[31] which limited the labeling to one time point. Using continuous bromodeoxyuridine (BrDU) labeling and dual-immunofluorescence detection, Lassman et al.[32] showed that the DNA synthesis is prominent in the urothelium, lamina propria, and interstitial cell population, and is almost never seen within the smooth muscle bundles (Figure 64.5). This prominent

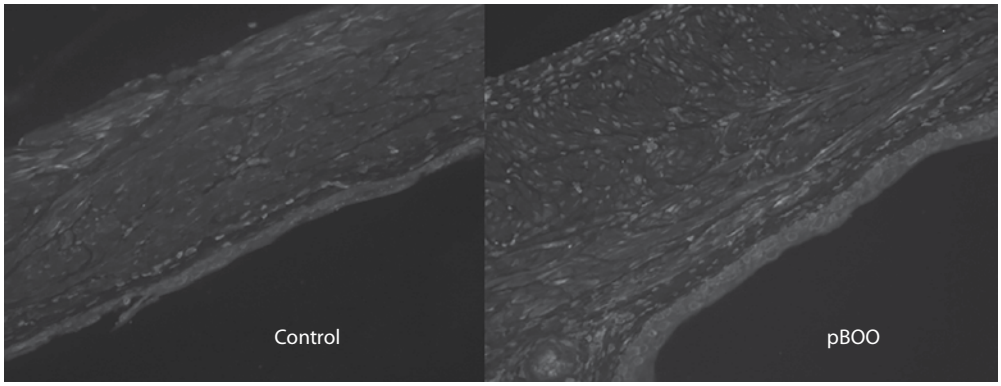

FIGURE 64.5 The sites of DNA synthesis in the bladder wall were determined in control mice and following partial bladder outlet obstruction using continuous BrDU uptake. Dual-immunofluorescence microscopy showed the sites of DNA synthesis (pink nuclei) to be predominantly contained within the interstitial cell population, and *not* within the smooth muscle population, as defined by staining against smooth muscle myosin heavy chain (green). This would suggest that DNA synthesis is occurring within the interstitial cells, and hence provide a means for increased collagen synthesis and matrix deposition. (From Lassmann J et al. *Am J Physiol Regul Integr Comp Physiol* 2008;294(1):R58–65. With permission.)

DNA synthesis within the areas of the bladder that are rich in fibroblasts ties in well with the impressive deposition of extracellular matrix elements that have been described in humans and experimental models. Experimentally, there is an increase in collagen synthesis in cultured bladder "smooth muscle" cells subjected to biaxial mechanical strain,[33] and this is mediated at the transcriptional level as shown by increased mRNA expression.[34] The caveat in these experiments done with cultured bladder cells in culture is that the cell type more likely represents a myofibroblast. The benefits of such a system are its simplicity and the ability to manipulate the variables more readily. Changes have also been described in the complex regulatory system that breaks down collagen. The matrix metalloproteinase enzymes may break down the extracellular matrix, and the tissue inhibitors of the matrix metalloproteinases (TIMPs) may in turn regulate them as a feedback mechanism. Peters et al. have shown TIMP expression to be increased within the bladder wall in a fetal sheep model of partial outlet obstruction, thus providing another mechanism for the dramatic increase in bladder wall fibrosis.[35] The clinical relevance of these observations is that this prominent deposition of extracellular matrix alters both the active and passive properties of the bladder wall.

Are there specific signaling pathways that are activated following outlet obstruction that lead to hypertrophy, and how might these be used for therapeutic benefit? The calcineurin–nuclear factor of activated T cells (NFAT) pathway represents one potential pathway to bladder hypertrophy, as demonstrated in a murine model of outlet obstruction.[32,36] Of the four existing NFAT isoforms, $NFATc_4$ has been shown by a CHIP on CHIP (chromatin immunoprecipitation ["ChIP"] with DNA microarray ["chip"]) analysis to bind to the *ctgf* promoter,[36] thus providing a second link to this profibrotic cytokine, which is upregulated following pBOO. Clearly, other pathways contribute to this remodeling, as shown by Schroder et al., who have shown that the mammalian target of rapamycin (mTOR) pathway is also mediating this hypertrophy.[37] These findings are of clinical relevance because cyclosporine A (a calcineurin inhibitor) and rapamycin (an inhibitor of mTOR) have been shown to protect the bladder in experimental pBOO models.[36,37] In time, it is hoped that this work will have clinical translational relevance in improving bladder function in this patient population.

Effects on the Upper Ureter, Renal Pelvis, and Kidney

Ultimately, as the bladder fails to adapt to its imposed workload (compensate), a sequence of molecular events results in which the bladder begins to retain larger volumes of urine. Because of this, the resting pressure in the bladder before voiding becomes significantly elevated, and this increased resting pressure is transmitted to the upper urinary tract over prolonged periods. *It is clear that elevated voiding pressures by themselves do not cause harm to the upper urinary tract*. Sillen et al. have documented extremely high voiding pressures in normal male infants or those with reflux and normal renal function.[38] *Thus, damage to the upper urinary tract occurs because of elevated intravesical storage pressures over prolonged time intervals*. The results of this are manifested in the resulting ureteral dilatation and rise in intrarenal pelvic pressures. Elevated bladder pressures are transmitted back to the renal pelvis under conditions of *high bladder volumes, noncompliant bladders, and a high urinary diuresis;*[39–41] *these conditions are met in patients with posterior urethral valves*.

Elevated renal pelvic pressures ultimately have a profound effect on renal morphology and function. A complete review of obstructive nephropathy is beyond the scope of this chapter; however, some basic concepts deserve mention. Obstruction impacts renal concentrating ability, glomerular filtration rate (GFR), and renal morphology. Numerous human and experimental observations support the notion that renal concentrating ability is diminished in the presence of obstruction.[42,43] This might occur as a result of damage to the luminal cells within the tubules, as shown in a study in which mechanical deformation of renal epithelial cells in culture was associated with apoptosis.[44] This might also reflect changes in blood flow to the medulla,[45] and a subsequent loss of the medullary concentrating gradient.[46,47] While these changes are probably of lesser significance in the fetal kidney that has poor concentrating ability, they have a profound impact in the older patient with posterior urethral valves who is left with pronounced polyuria and a compensatory polydipsia.[48] These changes also can account for the occasional patient who has a postobstructive diuresis following initial catheter placement in the neonatal intensive care unit (NICU).

Most boys with valves experience a drop in their GFR, although this is variable. Some anatomic variants dampen the pressure transmitted by the upper tracts to the kidney and thereby lessen renal damage. *When the full effects of high resting pressures are transmitted to the kidneys, fibrosis has been observed clinically and experimentally* [49] *both within the renal pelvis and within the renal parenchyma*. The cytokine transforming growth factor β (TGF-β) is associated with this fibrosis and is also secreted into the urine, providing a biological marker for the presence of obstruction.[50,51] There is also therapeutic potential in this observation, for in an experimental study, treatment with antibodies to TGF-β alone or in combination with an angiotensin-converting enzyme (ACE) inhibitor resulted in diminished renal fibrosis.[52,53] The deposition of the fibrosis is not necessarily uniform throughout the kidneys, which might reflect regional alterations in perfusion.

Genotypes and ESRD

Researchers have tried to determine if ESRD seen in boys with valves is solely a consequence of the obstructive uropathy or the result of delay in treatment in the fetal period. *Harrison et al. found that fetal surgical intervention for the infant with posterior urethral valves did not lead to improved renal outcomes, although it was associated with better pulmonary outcomes*.[54] However, these interventions were reserved for the most severe cases, and the authors concluded that by the time of intervention, the damage from obstructive uropathy may have become irreversible. An alternative explanation might be that obstruction alone is not the sole etiology of the ESRD, but that anomalies in the ureteral bud and nephrogenesis may

also contribute. The role of the angiotensin II receptor in ureteral and renal development is well established, and its targeted gene deletion may be associated with ureteral ectopia and associated renal hypoplasia.[55]

Given the central importance of the angiotensin receptor (ATR) in ureteral budding, branching, and renal development, several investigators have sought to study how the renin–angiotensin system (RAS) is altered in patients with posterior urethral valves. Components of the RAS where such genetic variability arises include ACE, angiotensinogen (AGT), and the ATR. Insertions and/or deletions within a fragment of intron 16 of the ACE gene account for up to 50% of the variability of the serum enzyme activity.[56] If all cases of ESRD associated with posterior urethral valves were attributable to obstructive uropathy alone, there should be no clustering of genotypes according to clinical outcomes. However, the distribution of the ACE I allele, which is associated with lower enzymatic activity, was much more likely to be seen in children with posterior urethral valves and renal insufficiency than it was in a normal population. Despite this observation, higher peripheral renin activity is observed in patients with posterior urethral valves than normal age-matched children.[57] This seeming discrepancy may arise because of the difference between the role of the RAS in development and renal branching, and its response in the postnatal period in the face of renal injury.

DIAGNOSIS

With the widespread use of screening antenatal sonography, the majority of patients with posterior urethral valves are being diagnosed in utero. It was initially hoped that this increase in diagnostic ability would lead to fetal intervention and better renal outcomes. Despite the widespread use of fetal sonography, there continues to be a high incidence of long-term renal failure in these patients. This suggests that by the time current imaging technology detects renal damage, it is already irreversible, or that the patient may have an at-risk genotype, or some combination of the two. Even with the widespread use of prenatal sonography, several series report that up to 10%–20% of boys present with symptoms such as urosepsis or urinary incontinence. In our own recent review of cases, 40% of patients presented beyond the neonatal period because of either a urinary tract infection or incontinence.[58] Possible explanations for this include a lack of access to prenatal care, a single screening ultrasound being performed at 19–20 weeks, and a lesion whose effects of the upper urinary tract may be progressive over time. One such example of a male fetus is shown in Figure 64.6, whose antenatal imaging was normal and yet who presented with incontinence and a rise in serum creatinine (Cr) as he failed to successfully toilet train.

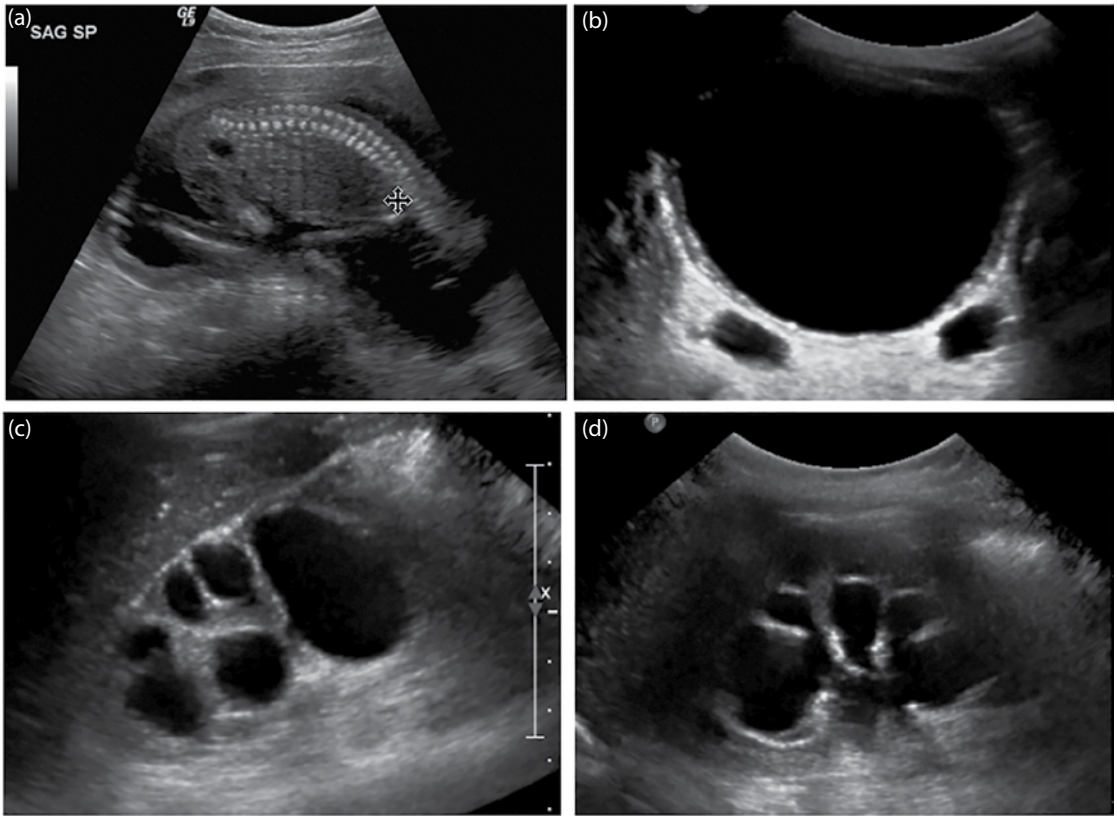

FIGURE 64.6 (a) The fetal sonogram of a boy showed no hydronephrosis and a normal bladder at the 23-week mark of gestation. However, at 5 years of age, this patient presented with urinary incontinence and a rising Cr. (b–d) His renal and bladder ultrasound demonstrated a thick-walled bladder and bilateral hydroureters (b). Severe hydronephrosis was noted in both kidneys, with cortical thinning worse on the right (c) than the left (d). He proved to have posterior urethral valves, after which his Cr declined to within a normal range. Such presentations are not uncommon.

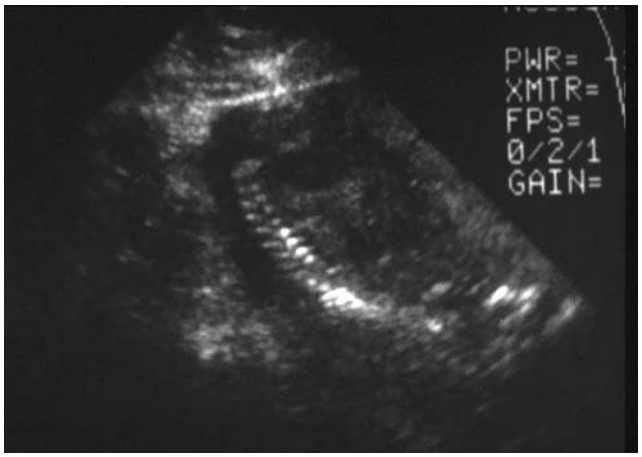

FIGURE 64.7 Fetal sonogram showing severe oligohydramnios. Note the lack of amniotic fluid between the spine and the uterine wall. Death occurred in the neonatal period from pulmonary hypoplasia.

Fetal Imaging

Screening sonography will usually detect a major obstructive uropathy at 18–19 weeks of gestation, and lead to further study with a higher-resolution ultrasound. The finding of a thick-walled bladder and bilateral hydroureteronephrosis in a male fetus suggests posterior urethral valves. However, ultrasonographers also see these changes in boys with the prune belly syndrome. One study suggests that sonography is accurate in making a diagnosis of posterior urethral valves in 50% of cases.[59] In addition to a determination of how much renal parenchyma is present, a critical factor in assessing the sonogram is the presence or absence of amniotic fluid. Oligohydramnios (Figure 64.7) is an ominous sign of advanced and severe obstruction. *In recent years, the role of sonography has been supplemented with the use of fetal MRI in highly selected cases* (Figure 64.8).[60] *The indications for fetal MRI in such a setting include bilateral hydroureteronephrosis, bladder wall thickening, and oligohydramnios*. In one study of early third-trimester gestations, the addition of the fetal MRI altered the initial diagnosis made by sonography in 30% of the cases.[61] Another study revealed MRI to be highly accurate in the assessment of total lung volumes (TLVs) in patients with genitourinary anomalies after 26 weeks of gestation, but similar predictability was seen using a determination of whether oligohydramnios was present or absent.[62] Further work will clarify the precise benefits this imaging can offer over conventional sonography.

IN UTERO MANAGEMENT: INTERVENTIONAL

Harrison's pioneering work in fetal intervention began with extensive experimental work in the fetal sheep model in 1978,[63,64] and the first clinical interventions took place in the early 1980s[65] with the hope of improving the renal prognosis. Open fetal surgical intervention using either a vesicostomy or ureterostomies was performed and shown to be technically feasible.[54] However, despite technical success in a majority of these cases, the incidence of renal insufficiency remained high.[15] However, intervention improved pulmonary function and the restoration of amniotic volume due to the internal stenting of the aspirated amniotic fluid.[66,67]

It was clear that not all boys with posterior urethral valves benefit from in utero intervention, because the severity of the obstruction from the valve is so variable. If one performs aggressive intervention in a population skewed toward advanced disease, as shown in Figure 64.1, the results are uniformly disappointing. Most boys have a good prognosis if they complete a normal gestation and have a neonatal valve incision. *Attempts to better stratify the at-risk group, in whom fetal intervention for obstructive uropathy would be helpful, led to the development of urinary sampling as a means of predicting which patient might benefit from this approach*. The ability to sample urine from the fetal bladder allows for analysis of

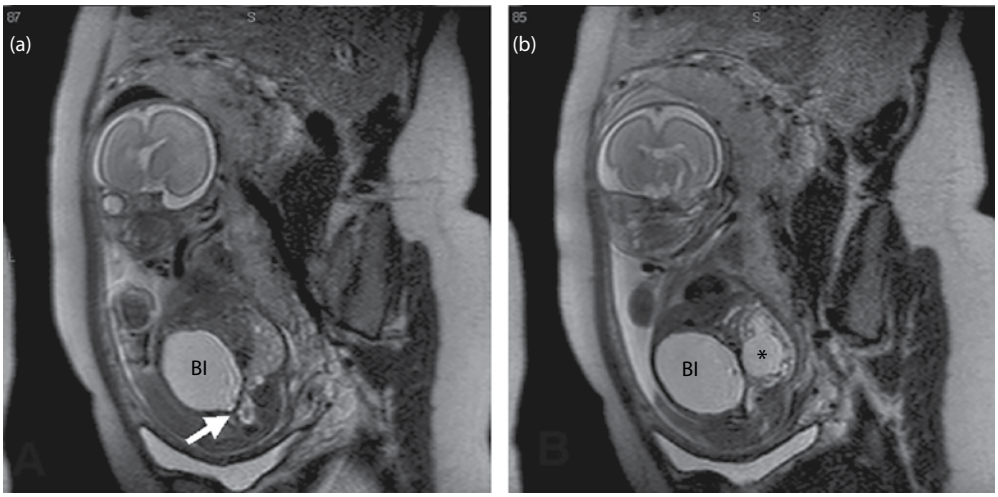

FIGURE 64.8 Maternal–fetal MRI showing moderate amniotic fluid levels and evidence of a dilated bladder (Bl), dilated posterior urethra (arrow) (a), and hydroureteronephrosis (*) (b).

electrolyte composition and testing for the expression of markers such as β_2-microglobulin. Under ordinary conditions, the fetal urine is hypotonic, which reflects the fetal kidney's poor ability to concentrate the urine. This is because proximal tubular function develops and active sodium transport results in a hypotonic filtrate. This hypotonic filtrate then passes on through the distal tubules with minimal reabsorption of free water. In contrast, in the older child, this hypotonic filtrate is concentrated by the absorption of free water via the aquaporin channels.[68] Glick et al. demonstrated that in the fetus with severe obstructive uropathy and renal dysplasia, a nearly isotonic urine was observed, which suggested significant problems with proximal tubular function, which mediates sodium reabsorption.[69] In contrast, with mild renal impairment, urine sodium, chloride, and osmolarity are hypotonic. There was initial optimism that urinary aspiration from the bladder with electrolyte and osmolarity analysis might predict long-term renal outcomes. *Favorable urinary electrolytes were deemed as follows: $Na^+ < 100$ mEq/L, $Cl^- < 90$ mEq/L, and an osmolarity below 210 mOsm/L. In the long term, fetal urinary electrolyte analysis still fails to separate those with a favorable renal prognosis from those in whom ESRD develops.*[15] The use of additional urinary markers, such as β_2-microglobulin, has also been investigated,[70] but none offer the perfect predictive test. Freedman et al. offered evidence that sequential bladder taps on 3 successive days might increase the predictive power of this method.[71] Despite this, in a recent review, even among those patients with favorable electrolyte patterns, the incidence of ESRD remained increased at nearly 30%.[72,73] In summary, *urinary electrolytes, if unfavorable, can predict the most severe cases of fetal obstructive uropathy seen with dysplasia. However, even patients with a favorable electrolyte pattern may progress to ESRD.* The pitfalls of this diagnostic dilemma have been reviewed by Elder,[74] and it remains an area for further research. Perhaps with the application of proteomics to urine samples collected from patients with known postnatal outcomes, a better marker of irreversible renal injury may be identified.[75]

Neonatal demise in patients with severe posterior urethral valves does not result from ESRD, but rather from pulmonary hypoplasia.[76] The etiology of this appears secondary to the loss of the mechanical distending forces provided by the aspiration of the amniotic fluid.[66,67] This experimental work formed the basis for clinical trials of amniotic fluid replenishment, which have resulted in improved neonatal pulmonary function.[77,78] In another smaller review of fetal intervention, Coplen et al. reported a high incidence of ESRD in shunted patients, but no evidence of respiratory compromise. However respiratory compromise was seen in those patients who were not shunted.[79] To summarize, *the hopes of fetal intervention for the prevention of renal failure have not been realized, but pulmonary function has improved in the most severe cases. Improved criteria might allow for the promise of fetal intervention to a small and highly selected population of patients with obstructive uropathy.*[71] Such efforts should be limited to those centers with expertise in this complex procedure and the antepartum care.

IN UTERO MANAGEMENT: OBSERVATIONAL

We recommend observing most patients with an in utero diagnosis of posterior urethral valves with serial sonograms to monitor the degree of urinary tract dilatation and the amount of amniotic fluid. Allowing these gestations to progress as close to term as possible optimizes pulmonary development. Communication between the obstetrical team and the pediatric urologist is always helpful to establish a clear plan of action for the family, and the healthcare team. The potential for good renal function and a near-normal lifestyle should be emphasized, as well as the small but real potential for long-term renal failure.[80] In severe cases where ESRD is likely, families may opt for termination of pregnancy.[81] The need for antibiotic prophylaxis, a renal bladder ultrasound, and voiding cystourethrogram (VCUG) in the neonatal period must be communicated to the family and referring physicians.

DIAGNOSIS IN THE OLDER CHILD

Although less common in this era of prenatal sonography, boys with valves still present with a history of either urinary tract infection, retention, or incontinence (Figure 64.6).[2,82–84] Not surprisingly for so diverse a condition, there is a case report of a boy presenting with valves despite a normal prenatal sonogram at 30 weeks' gestation.[85] *Boys with a urinary tract infection should have a renal and bladder ultrasound to exclude major underlying structural problems. If the boy has a febrile urinary tract infection or retention, we add a VCUG.*

Some older boys with valves have only urinary incontinence. In some cases, it is hard to single out the one boy who has a valve from the many with dysfunctional voiding and wetting from volitional urinary retention. While isolated nocturnal enuresis or an occasional daytime episode of wetting associated with delays in voiding is not cause for alarm, *the boy who presents with regular day- and nighttime wetting should trigger a suspicion of bladder outlet obstruction.* A screening renal bladder ultrasound should be done to exclude associated bladder wall thickening and assess the upper tracts, followed by a uroflow study and determination of postvoid residual. *The presence of a thick-walled bladder and obstructive uroflow pattern should lead to a VCUG being performed to rule out the presence of posterior urethral valves or a stricture.* Once these studies have ruled out any anatomic blockages, treatment of the dysfunctional voiding may proceed. Rarely, boys with valves have been treated for dysfunctional voiding for several years with growing frustration at the lack of progress—hence the importance of maintaining a high index of suspicion for this diagnosis in the setting of a clinic filled with incontinent children, the vast majority of whom do not carry this diagnosis.

Postnatal Imaging

We prescribe antibiotic prophylaxis for the neonate we suspect may have posterior urethral valves prior to

postnatal imaging. Imaging begins with a renal and bladder ultrasound, which may be diagnostic. We order a VCUG as soon as possible if the ultrasound has any features that suggest a possibility of posterior urethral valves, such as a thick-walled bladder or hydroureteronephrosis.

Ultrasound

The presence of a dilated posterior urethra, thickened bladder wall, bilateral hydroureteronephrosis, and cortical thinning in a newborn boy is suggestive of valves (Figure 64.9). In some cases, the hydroureteronephrosis is limited to one side and with an associated cystic- or dysplastic-appearing kidney. This represents the valves, unilateral reflux, and renal dysplasia (VURD) syndrome,[86] in which one renal unit absorbs the brunt of the high pressure and loses function, while the opposite side is spared and undergoes compensatory hypertrophy (Figure 64.10). Ultrasound examination may also detect the presence of urinary ascites. In addition to a thick-walled bladder, there may also be an associated diverticulum (demonstrated on the VCUG in Figure 64.10). *These pressure pop-off mechanisms are associated with better long-term renal*[86,87] *and bladder*[88] *function*.

In addition to noting the degree of upper tract dilatation, the intrarenal echogenicity can also serve as a valuable clue to the renal prognosis. Within the normal kidney, there are substantial differences in the echogenicity observed between the renal medulla and cortex (Figure 64.11). *In contrast, with substantial renal damage, there is a loss of this corticomedullary differentiation* (Figure 64.11). The loss of this corticomedullary differentiation suggests a more ominous renal prognosis.[89,90]

VCUG

The VCUG remains the cornerstone of achieving an accurate diagnosis of posterior urethral valves. Sometimes it is difficult to pass an 8 French feeding tube (Figure 64.12), which may coil within the dilated prostatic fossa. Using a coudé-tip catheter allows for the passage of the catheter over the hypertrophied bladder neck. Once the radiologist fills the bladder and the bladder begins to contract, the catheter is withdrawn to allow fluoroscopic observation of the entire urethra. The characteristic valve cusp appears at the inferior aspect of the dilated prostatic urethra and appears identical to the leaflets seen at the time of cystoscopy (Figure 64.13). Although the diagnosis of valves is

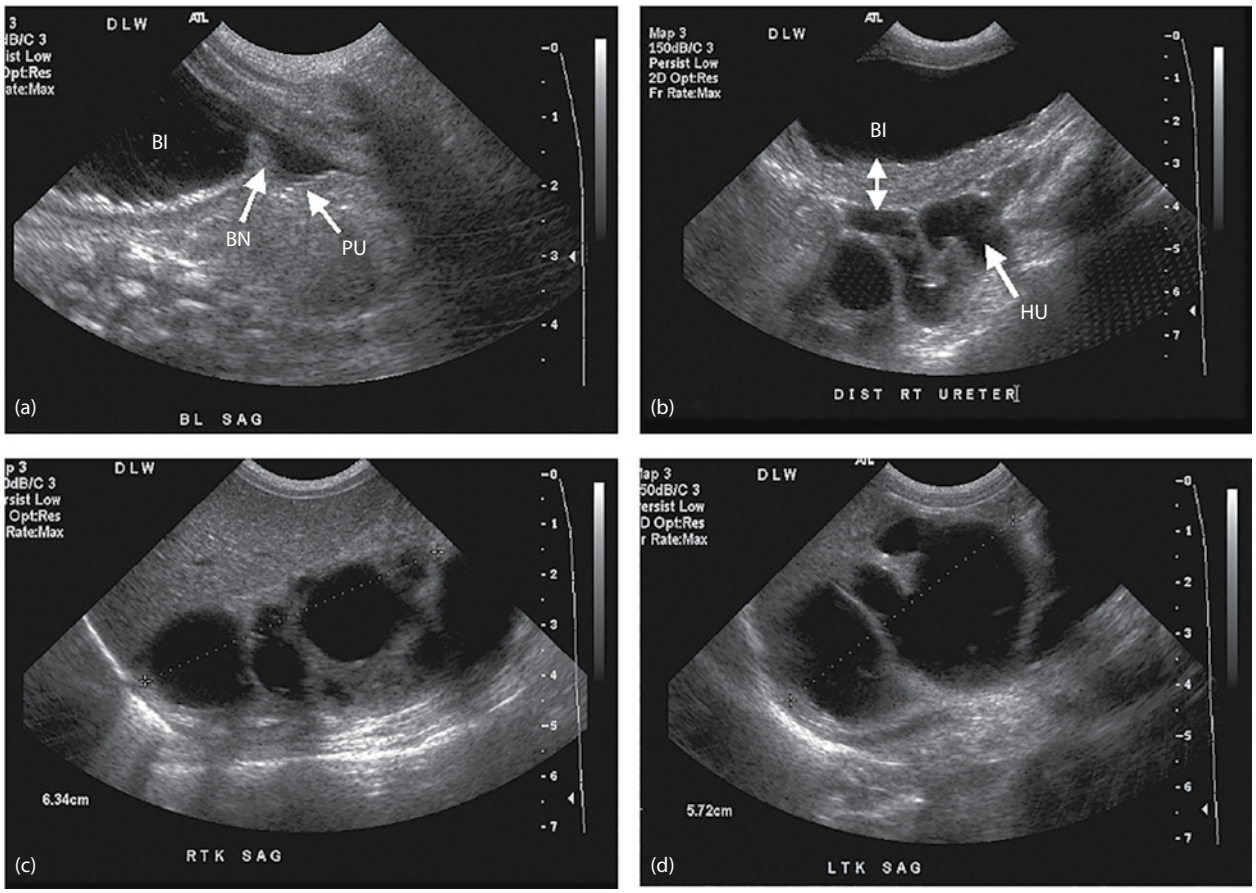

FIGURE 64.9 This postnatal ultrasound demonstrates the classic findings of severe posterior urethral valves. (a) The distended bladder (Bl) can be traced in this sagittal view down to the level of a dilated bladder neck (BN) and dilated posterior urethra (PU). (b) The dilated bladder has a very thick wall (arrows) and associated severe hydroureteronephrosis (HU). (c and d) Both kidneys show severe cortical atrophy.

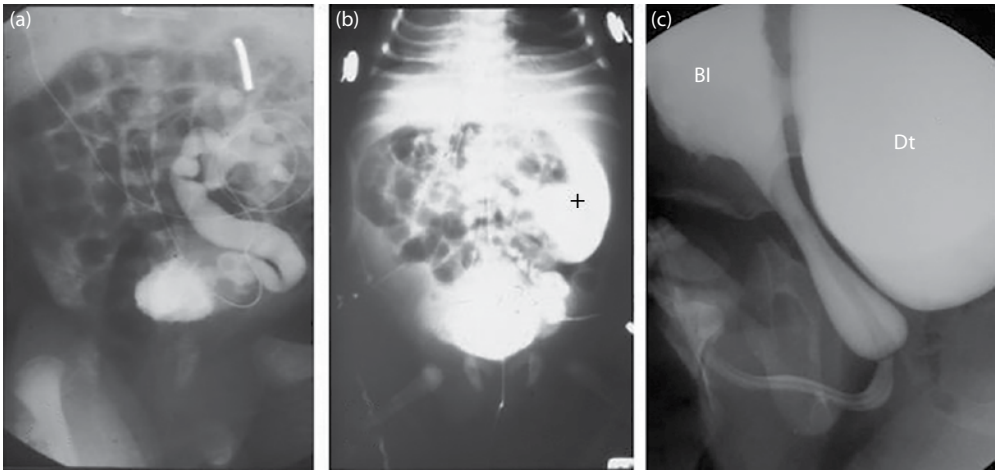

FIGURE 64.10 Pressure pop-off mechanisms that serve to vent elevated intravesical pressure and preserve renal function have been well described. (a) Example of the VURD syndrome in which the left renal unit has high-grade reflux and dysplasia; this spared the right kidney. (b) Extravasation into the perinephric space (+) following a forniceal rupture may also occur. (c) The large bladder diverticulum spared this patient's renal function. Bl, bladder; Dt, diverticulum.

not affected by having the catheter in place during micturition (Figure 64.10c), it is best to have fluoroscopic voiding views free of any interference.

Sometimes it is not clear from the VCUG whether one is seeing a posterior urethral valve or contraction of the striated external sphincter. It is critical to view each image provided to find a view that demonstrates a relaxed external sphincter. In this case, "real-time" fluoroscopy is useful by personally observing the VCUG, if possible, or asking for a video recording. If any doubts remain as to whether the narrowing is physiologic or anatomic, we perform cystoscopy to exclude the presence of a valve leaflet. Similar concerns may arise on a postoperative VCUG following valve incision. In one illustrative case, initial views showed a narrowing of the distal aspect of the prostatic urethra (Figure 64.14b) that opened widely on subsequent views (Figure 64.14c).

The VCUG may also reveal the presence of unilateral or bilateral reflux. *Unilateral reflux may occur in a dysplastic and nonfunctioning kidney, and serve as a pressure pop-off mechanism.*[86,91] *Similarly, a large diverticulum may also serve as a venting mechanism and confer a better renal prognosis. We do not excise these diverticula. We believe that they provide low-pressure storage capacity unless urinary retention or infection intervenes.* We have illustrated these concepts with the cases in Figure 64.10.

Nuclear Medicine

If high-grade reflux into one kidney is associated with a thinned renal parenchyma, a mercaptoacetyltriglycine (MAGIII) renal scan will allow for quantification of function. However, the automatic removal of such kidneys is unwise unless infection forces the issue. Such dilated systems serve as low-pressure pop-off mechanisms and should be preserved if possible. Scans are often ordered to rule out ureterovesical junction obstruction, but in such highly dilated systems, the washout times will always be

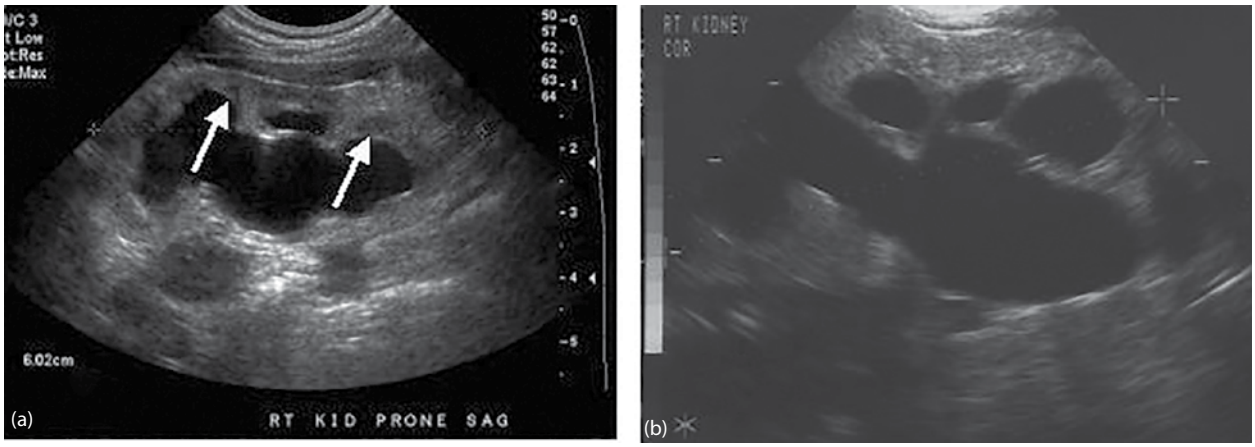

FIGURE 64.11 (a) Differences in renal corticomedullary echo density or differentiation are a favorable prognostic sign. The arrows point to areas within the medullary region that are of distinctly lower density than the surrounding cortical regions. Sometimes these areas are mistaken for a fluid-filled calyx. (b) In contrast, a renal sonogram shows severe hydronephrosis and a renal parenchyma that is uniformly dense and shows no corticomedullary differentiation. Fifteen years later, this patient is in renal failure.

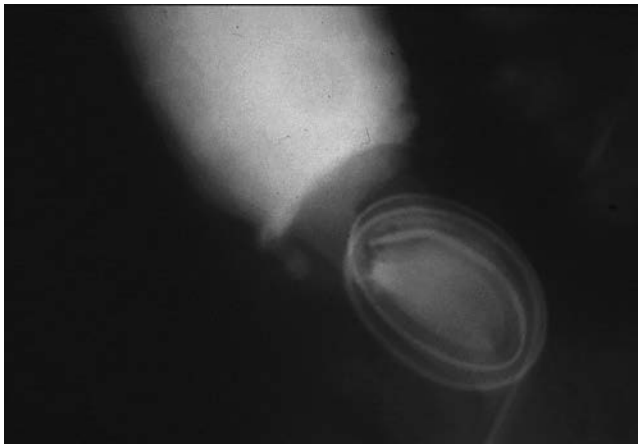

FIGURE 64.12 The challenge of placing a catheter in a dilated posterior urethra is usually circumvented by using a coudé-tip catheter. Occasionally, even a coudé-tip catheter will coil in the posterior urethra, and require fluoroscopic placement. This is useful for the older boy with valves who is going to initiate CIC.

prolonged, which makes the test less useful. For this reason, renal MAGIII scans need not be ordered routinely, but should be restricted to a small subset of patients.

Management Options

Initial Management in NICU

Following delivery, a healthy neonate with good pulmonary function can safely bond with his mother and father. Within hours, as the neonate is transferred to the NICU, we obtain an ultrasound, and if the findings are consistent with valves, we place a feeding tube in preparation for the VCUG. We then start antimicrobial prophylaxis with amoxicillin. *A child who is stable from a pulmonary standpoint can then be prepared for valve ablation often within 48–72 hours of life.*

If the boy has pulmonary hypoplasia and complex ventilatory requirements, prematurity precluding endoscopic manipulation, or significant postobstructive diuresis, we delay the valve incision and opt for a period of urethral catheterization. Sometimes in these settings, the infant's serum Cr rises above the maternal Cr as the degree of renal impairment becomes manifest. Usually, the diuresis is physiologic, but rarely, the rise in Cr may reflect prerenal dehydration that follows postobstructive diuresis. In these situations, we recommend maintaining catheter drainage and allowing the medical condition to stabilize.

Surgical Aspects

With the major advances that have taken place in fiberoptic technology, it is now possible to incise posterior urethral valves in all but the smallest premature neonates. Many approaches to valve incision have been described.[92] A bugbee electrode can be passed through a 7.5 or 9 French neonatal cystoscope to apply cutting current to the valve leaflets at the five, seven, and twelve o'clock positions (Figure 64.15) or at the twelve o'clock position alone. Valve incision requires only that the surgeon disrupt the integrity of the valve; overzealous attempts to fully excise the valve raise the risk of stricture formation.

We consider performing a vesicostomy as the initial surgical intervention in the very premature neonate whose urethra will not accommodate an endoscope; trauma from a large cystoscope can induce a urethral stricture. We also consider this approach in a neonate whose Cr has risen despite successful catheterization. In this setting, the vesicostomy minimizes lower urinary tract storage pressures and optimizes GFR.[93,94] We believe that a vesicostomy does not place the bladder at total rest; in fact, the bladder does fill, and undergoes partial cycling, albeit at much lower pressure. A vesicostomy allows for venting of high intravesical pressures as they develop, thus minimizing any transmission of pressure back toward the kidneys.

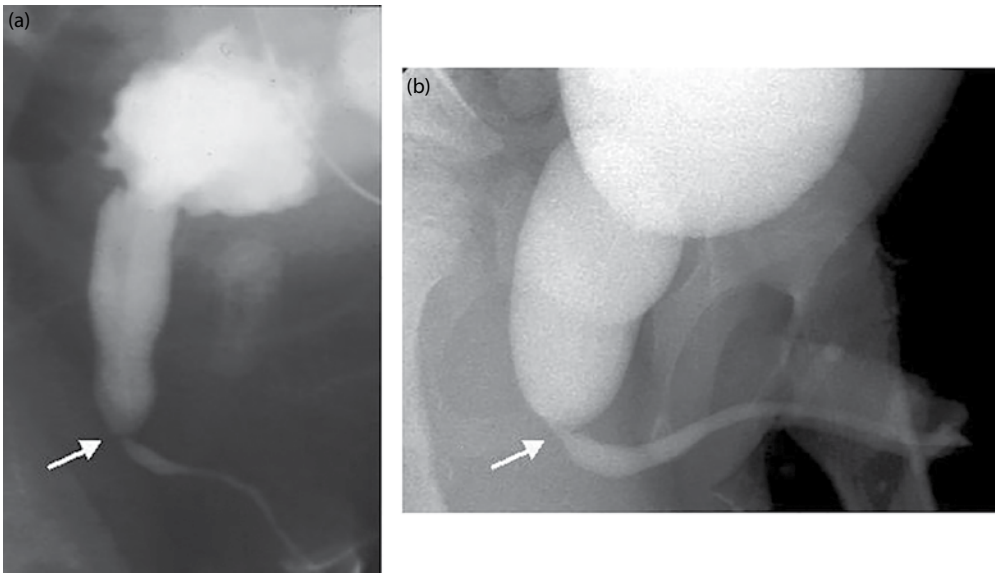

FIGURE 64.13 (a and b) The classic valve cusps associated with type 1 posterior urethral valves (arrows) are demonstrated in these two VCUGs.

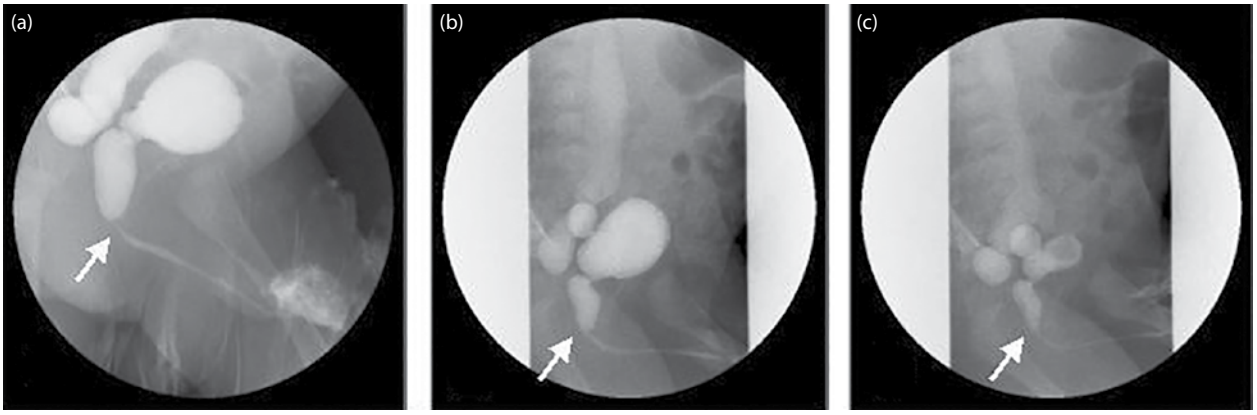

FIGURE 64.14 (a) The classic type 1 posterior valve is shown preoperatively (arrow). (b) The postoperative appearance of a VCUG for a patient 3 months following valve resection demonstrates what might appear to be a residual valve leaflet (see arrow). (c) However, full review of all the fluoroscopic images reveals that this narrowed area opens up when the striated external sphincter is relaxed.

One long-standing controversy in the management of patients with posterior urethral valves revolves around the use of high urinary diversion. Historically, a child whose renal function failed to improve, or even worsened, following valve ablation might undergo bilateral ureterostomy or pyelostomy. Following the surgery, the Cr level often decreased, and thus high diversion has had its advocates.[94,95] Some believe that boys with severe outlet obstruction develop a secondary obstruction at the ureterovesical junction due to potential obstruction of the dilated ureter as it passes through the severely thickened bladder wall. If this were true, then high diversion would potentially reduce risk of renal damage from ongoing high pressure despite valve incision. If, in such a setting, a nephrostogram is performed, it is possible to demonstrate an "obstruction" at the ureterovesical junction (Figure 64.16). *Although there are still centers where persisting dilatation of the upper urinary tract following successful valve ablation leads to consideration for upper urinary diversion, most pediatric urologists do not recommend high diversion despite some clinical evidence that resulting bladder function is good following undiversion.*[94] The

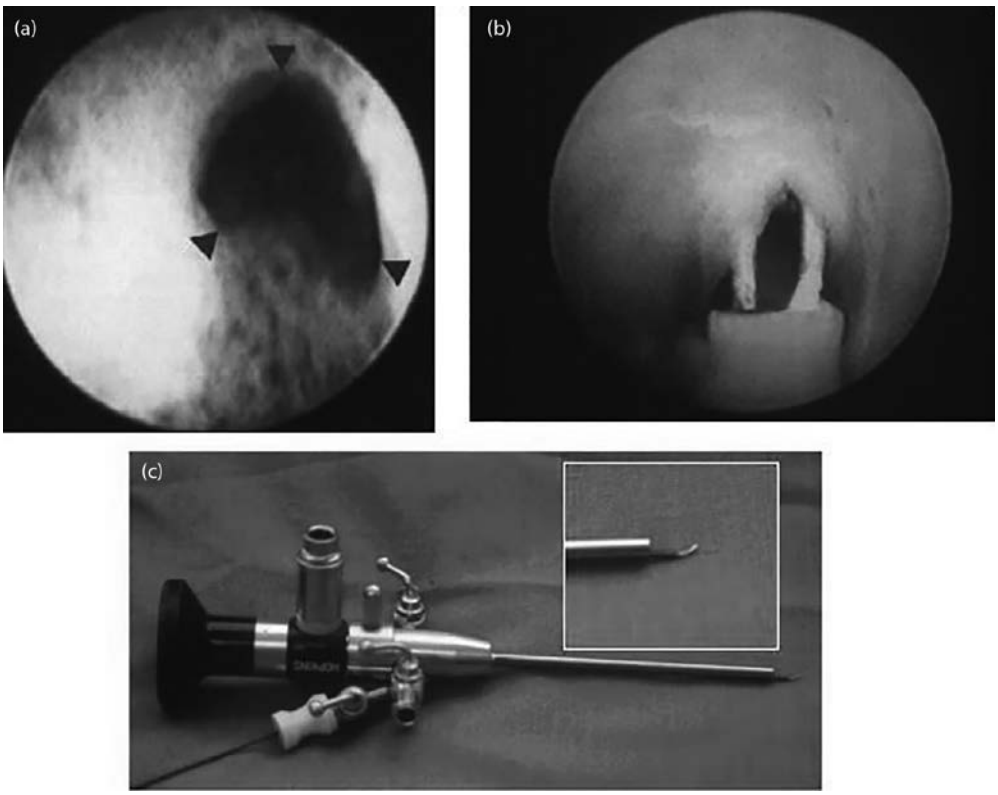

FIGURE 64.15 Incisions may be made at the twelve, five, and seven o'clock positions (a) using either a resectoscope (b) in an older child or a bugbee electrode delivered by a 9 French cystoscope in the neonate (c).

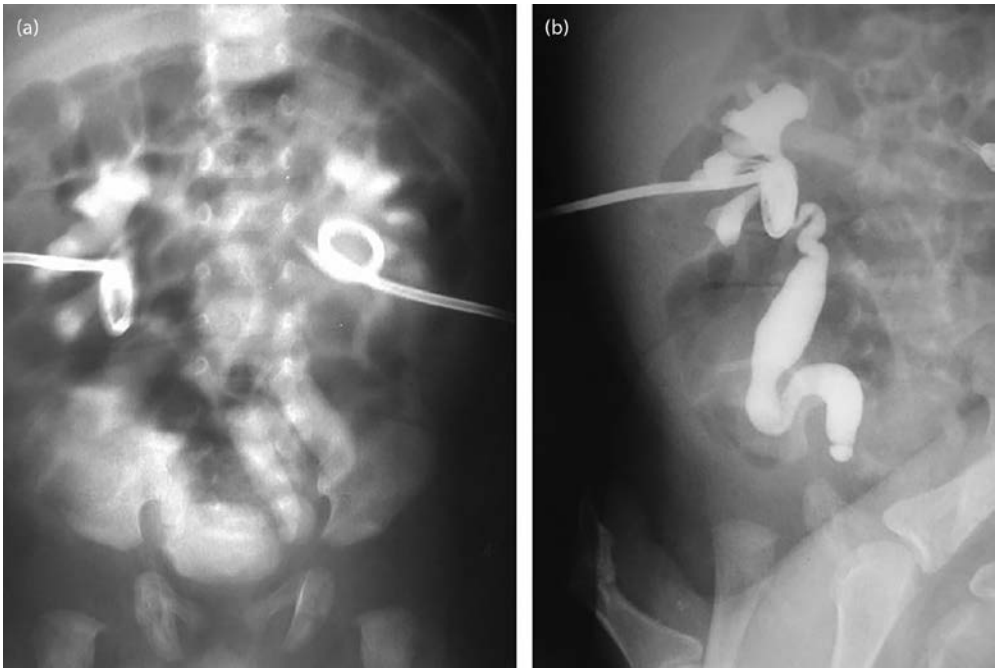

FIGURE 64.16 Upper tract imaging was ordered in this boy because the hydronephrosis failed to respond to primary endoscopic valve ablation. (a) The intravenous pyelogram reveals bilateral hydroureteronephrosis with delayed washout on the left. (b) An antegrade nephrostogram revealed a distal ureteral narrowing with impedance of flow into the bladder. At the time of these studies, this patient was 2 months old and had a serum Cr of 0.7. Advocates for high urinary diversion to maximize GFR would note that the increased resistance to drainage shown in panel B supports their approach. Advocates of the watchful waiting approach would counter with the following arguments: (1) If the nephrostomy tube were clamped, and one waited, contrast would flow into the bladder over time, because this is not a complete obstruction. (2) As the bladder experiences repeated filling and emptying cycles, it will heal, and as the wall thickness diminishes, the resistance to antegrade flow will diminish. Our recommendation in this case was for the maintenance of antibiotic prophylaxis, circumcision, and serial imaging of the upper tracts at increasing intervals as the upper tracts decompressed.

alternative point of view is that high diversion interrupts the normal bladder cycle of filling and emptying,[96] resulting in a stiff fibrotic bladder that is more difficult to rehabilitate later on prior to transplantation.[97–99] This view is supported in part by experimental evidence in a dog model of urinary diversion and undiversion, which demonstrated detrimental physiologic and pharmacologic changes that take place when the bladder was prevented from cycling.[100] Similar findings were noted in a fetal sheep model with increased expression of extracellular matrix elements[101] and increased apoptosis[102] following high diversion.

Circumcision

We recommend circumcision in boys with valves. Wiswell's data suggest that febrile urinary tract infections are more commonly seen in uncircumcised males.[103,104] The consequences of urinary tract infection superimposed on a dilated urinary tract with stasis and renal insufficiency should be enough to give every urologist ample cause to encourage circumcision in this setting.

Nephroureterectomy

The traditional approach to the management of patients with unilateral high-grade reflux and associated dysplasia (the VURD syndrome)[86] called for an initial valve incision, followed by a nephroureterectomy. However, we no longer remove poorly functioning kidneys unless recurrent urinary tract infections are definitively localized to the poorly functioning unit. In our experience, this is very rare. We believe the low-pressure venting into the nonfunctional system places less stress on the compromised valve bladder. For boys in renal failure, the native kidneys maintain fluid balance; renal failure with moderate polyuria is easier to manage than anuria. *It has been our experience that native nephrectomy is rarely required in these boys. If a nephrectomy is required, the ureters should be left behind for use in subsequent reconstructions.*[105]

Ureteral Reimplantation

While up to 50% of patients presenting with valves show signs of vesicoureteral reflux on their initial VCUG,[93] successful valve ablation and bladder cycling lead to resolution in the majority of cases. Glassberg and coworkers have argued for management based on urodynamic data. He notes that treating residual voiding dysfunction often leads to reflux resolution in this population.[106] If bladder function is optimal, then reimplantation can be performed succesfully.[107] It is well established that reimplantation of dilated ureters into thick-walled bladders with associated voiding dysfunction carries a higher complication rate.[108] Thus, if correction of reflux in this patient population is desired, some consideration should be given to endoscopic injection.[109] *In our own experience, ureteral*

reimplantations are almost never required in circumcised boys with successfully incised valves and may compromise bladder compliance or, worse, potentially further compromise a failing kidney.

Surgical Complications

Surgical complications from endoscopic valve ablation are rare with the current generation of smaller high-resolution fiber-optic endoscopes. The feared complication of past years was a stricture induced by passing too large an instrument through a tiny urethra. We almost never see this complication now that we have pediatric cystoscopes as small as 7.5 French with a side port for a bugbee electrode. This is preferable to using the resectoscope, which is a larger instrument. *In the very small infant, in the rare event that available endoscopes cannot pass through the urethra, we consider a vesicostomy with a plan for delayed valve incision.*[92]

Short- and Long-Term Outcomes of Posterior Urethral Valves

Short-term complications seen following valve incision may include urinary retention and renal failure.[93,110] If voiding is not complete and urinary tract infection ensues following valve incision, short-term use of clean intermittent catheterization (CIC) may become necessary. In general, if urinary retention is noted postoperatively, catheterization for 24 hours, followed by a repeat voiding trial, is nearly always successful. The number of valve patients who have true myogenic failure is small.[111]

In some boys, the neonatal course is complicated by renal failure. In many of these cases, the more immediate life-threatening problem is respiratory failure brought from hypoplastic lungs (Figure 64.1). Fetal sonography allows for an opportunity to minimize pulmonary complications by either shunting or amniotic fluid infusions. Extracorporeal membrane oxygenation (ECMO) has been used for these boys until they can be managed with conventional ventilatory support,[112] but the majority of these patients will develop ESRD and require renal transplantation later. Transplantation in the first year of life is rarely needed and should be a last resort. *While technically feasible, the discrepancy between the organ size and the total body volume of the recipient makes such procedures more challenging and higher risk than for older patients.* For this reason, as well as the desire to minimize the years of immunosuppression, *every effort is made to optimize renal function, avert dialysis, and let the child develop without the transplant as long as possible.*

Approximately 15%–30% of patients with posterior urethral valves go on to develop ESRD, depending on the series.[113] Studies suggest that if by 1 year of age the serum Cr has reached a nadir value of 0.8 or less, ESRD will be avoided.[93] Despite severe cortical thinning on sonography, many patients will see their Cr drop below 1.0 only to return with ESRD later in life. What can predict such a transition to ESRD? Some have suggested serial Cr measurements and a derivation of velocity with which the Cr drops.[114] Pulido et al. measured the renal parenchymal area from the initial ultrasound and demonstrated that for those patients with severe cortical thinning, a total parenchymal area of less than 12.4 cm^2 defined the cutoff for progression to ESRD by 6 years of age.[58] For the patients whose Cr at 1–4 weeks of age ranged from 0.8 to 1.1, the cohort whose renal parenchymal volume fell below 12.4 cm^2 was at far greater risk of ESRD by 6 years of age.[58] These findings must be validated in a larger multicenter study. The ability to identify the high-risk cohort for progression to renal failure would allow for the design of trials of medical intervention in the neonatal period with the goal of preventing or delaying the onset of ESRD. We suspect that the patients with low renal parenchymal volumes whose Cr values drop have no renal reserve, as they are perfusing all the limited number of glomeruli their kidneys possess.

If renal insufficiency is present in the neonatal period, there is usually enough GFR to support growth and development. Both the pediatric urologist and nephrologist must work together to closely follow boys whose Cr approaches these values. On occasion, these boys suffer from tubular acidosis and require bicarbonate replenishment. For those with more advanced renal insufficiency, growth hormone may be required. As the renal failure advances, calcium, parathyroid hormone, and bone development must be closely monitored. Long before the time for transplantation approaches, the urology and nephrology team must begin to address the function of the lower urinary tract, and its ability to safely sustain an allograft with low storage pressures.

Most series report a substantial delay in the acquisition of daytime and nighttime continence for all patients with valves.[93,110] For patients with less severe valves, the bladder and renal functions combined allow for continence usually around 6–7 years of age. However persistent urinary incontinence is an ominous sign in patients with a diagnosis of posterior urethral valves.[115] Given the pathophysiology of upper and lower urinary tract obstruction outlined at the beginning of this chapter, this incontinence is more readily understood. Because of the bladder wall fibrosis and poor storage capabilities, an increasing volume of urine is stored at higher pressures within the upper urinary tract. The severe polyuria that these patients exhibit due to distal tubular injury in utero worsens this problem. Ironically, the boy himself may also unwittingly aggravate the condition in his desire to be dry. As he struggles to achieve dryness by suppressing the desire to void, and retains urine, he contributes to upper tract dilatation and increasing storage pressures. For many boys, a regimen of timed voiding is effective. In others with upper tract dilatation, double voiding will safely result in dryness. Instructing the boy to void in the ultrasound suite, while assessing his bladder with pre- and postvoid views of the kidneys, ureters, and bladder, provides a powerful teaching tool for the boy, who will benefit from double voiding.

It has become clear in recent years that for many of these patients, overnight catheter drainage[116,117] and CIC will provide continence, lower storage pressures, and preserve renal function. For all these reasons, *a critical time to follow a boy with valves closely is around the time the child begins to express an interest in potty training.*

Videourodynamics

For the valves patient who has persistent urinary incontinence, or is approaching ESRD, videourodynamics offer an invaluable tool to optimize the chances for achieving dryness[106,118] *and for successful transplantation*. Prior to performing videourodynamics, it is essential to have the patient and family complete a thorough diary that includes not only the urinary output, but also the fluid intake. This helps to determine the average urinary volume produced on an hourly basis by day and night, and what voiding frequency will be required. *In contrast to conventional urodynamics, a videourodynamics study will help to determine what part of storage capacity is provided by the bladder and compare that with what is contributed by the upper tracts*.

We have demonstrated this concept with the study shown in Figure 64.17. This study, if done conventionally, would suggest that the boy has a very compliant bladder. In fact, when the video images are considered, it is clear that the bladder has poor compliance and there is high-grade reflux early in filling. The high-grade reflux into his native kidneys augmented this boy's storage capacity and masked poor bladder compliance. Despite attempts at double and triple voiding, his diurnal urinary incontinence persisted in part due to his polyuria. He resisted our attempts to teach him urethral CIC, which is typical in this population of boys with a sensate perineum and a dilated posterior urethra (Figure 64.12). Based on this study, we recommended an appendicovesicostomy to allow intermittent catheterization every 2–3 hours by day, and overnight catheter drainage. As long as this boy was compliant with his daytime catheterization schedule, he remained dry. Following transplantation, he remains continent due in large part to the improved concentrating ability of his allograft. In this case, the videourodynamics study altered this boy's care in two ways. First, the study made it clear that native nephroureterectomy would compromise his ability to achieve safe storage pressures. Second, the large residual urine measured by the study reflected storage in his upper tracts that would not respond to double-voiding regimens. Given these findings, clean catheterization via an appendicovesicostomy offered him the optimal management for achieving dryness in the short term, while preparing for the inevitable renal transplant that followed.

Postobstructive Diuresis

Boys with a history of posterior urethral valves often have persistent dilatation of the upper urinary tract that worsens as they begin to toilet train. For some boys, the imposition of daytime dryness achieved by delaying voiding and conscious use of the external sphincter places additional burden on the upper tracts. This worsens during sleep. What produces a reward for the child in terms of dry sheets in the morning and clean underwear at the end of the day may contribute to worsening of renal function. For some boys, this leads to a cycle (Figure 64.18) in which increasing bladder storage pressures result in higher renal pelvic pressures. This in turn aggravates renal medullary concentrating ability, which is already compromised,[48] and thus results in additional diuresis.

Clinical and experimental evidence support these concepts. In a videourodynamics assessment of partial bladder outlet obstruction, decompensated rabbit bladders had good compliance, defined as $\Delta V/\Delta P$. They also required much larger volumes (with a higher prevoid baseline pressure) to initiate their voids, which were small and associated with high residuals. Within this group, the postvoid residual urine recorded exceeded the infused volume.[119]

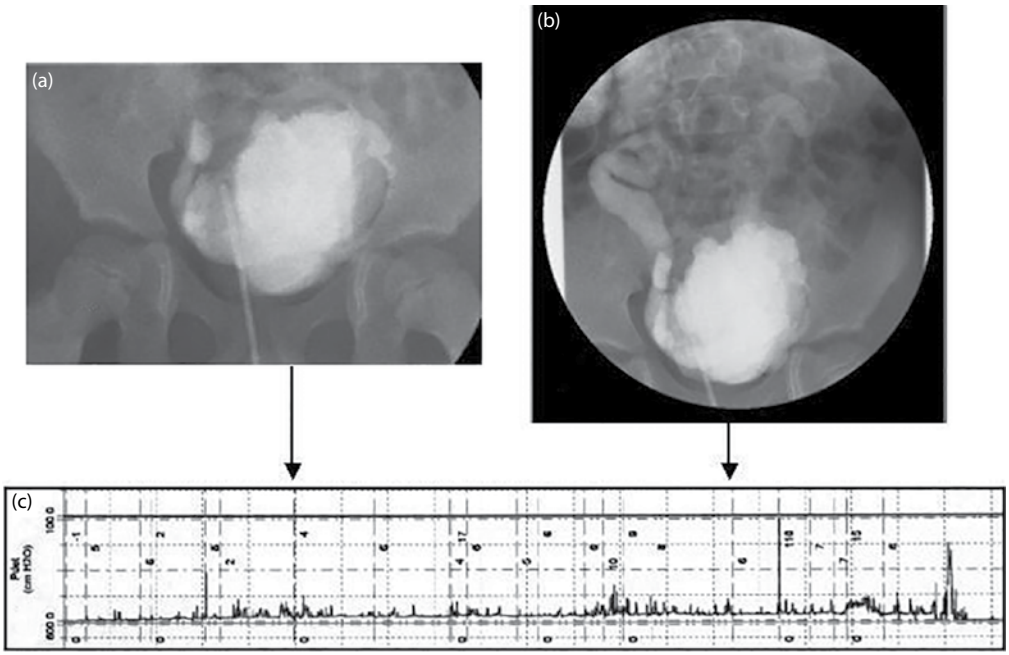

FIGURE 64.17 (a and b) This videourodynamics study demonstrates the benefit of the fluoroscopic examination. (c) This appears at first glance to be a very compliant cystometrogram; however, close examination reveals that compliance is augmented by the reflux into the upper tracts (b).

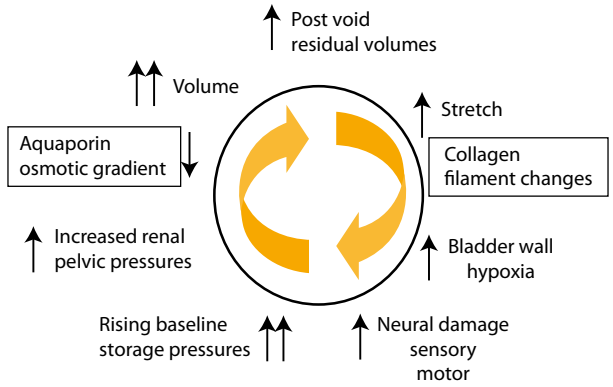

FIGURE 64.18 Schematic representation showing the integration of upper and lower urinary tract dysfunction in boys with posterior urethral valves. The cycle of gradual increasing postvoid residual volumes leads to increased resting prevoid pressures, which in turn lead to increasing renal medullary pressures. The resulting loss of concentrating ability results in increasing diuresis that aggravates the cycle by subjecting the bladder to increasing stretch.

This led us to consider these cystometrograms on an individual basis, and to classify them according to their baseline pressure before voiding. For the subset of obstructed bladders (30%) in which the baseline pressure exceeded 10 cm H_2O, the postvoid residual urine exceeded the infused volume by an average of 30 cc (Figure 64.19). How could the residual volume exceed the infused volume by nearly 40%? In performing these experiments, we emptied the bladder under fluoroscopic control before initiating slow-fill cystometry at 1–2 cc/minute. During the filling period, the diuresis from the upper tracts was pronounced in those bladders with an elevated baseline pressure before voiding. Although the majority of these bladders demonstrated "good compliance," these rabbits were spending most of their time at the far right of their cystometry curves, and thus subjecting their upper tracts to the same higher baseline pressure. This postobstructive diuresis was also observed in 30% of the rabbits following reversal of outlet obstruction in a subsequent group of experiments.[120]

We have observed similar findings in boys with posterior urethral valves. During a videourodynamics study of a boy with urinary incontinence following valve ablation, we noted that despite having initiated the study by aspirating all urine from the system, the postvoid residual urine exceeded the volume infused. We also observed this phenomenon in another boy with valves in whom we had created a unilateral end-cutaneous ureterostomy. We recorded this boy's ureterostomy output and correlated it with the catheterization status of the bladder. When this boy slept without an indwelling catheter, we recorded larger volumes of urine from the ureterostomy. In contrast, when sleeping with an indwelling catheter, the overnight volumes recorded from the ureterostomy dropped by almost 40%. This finding supports our conclusion[116] and that of others[117,121,122] who feel that *overnight catheter drainage can eliminate a substantial volume, and hence pressure burden, on the upper tract* (Figure 64.20). Taken over a period of time, and with recovery of some concentrating ability, the total 24-hour urine volumes often drop, both offering the benefits of improved daytime continence and optimizing renal function.

Pretransplant Evaluation

The pediatric urologist caring for these boys must continue to remain actively involved with the nephrology transplant

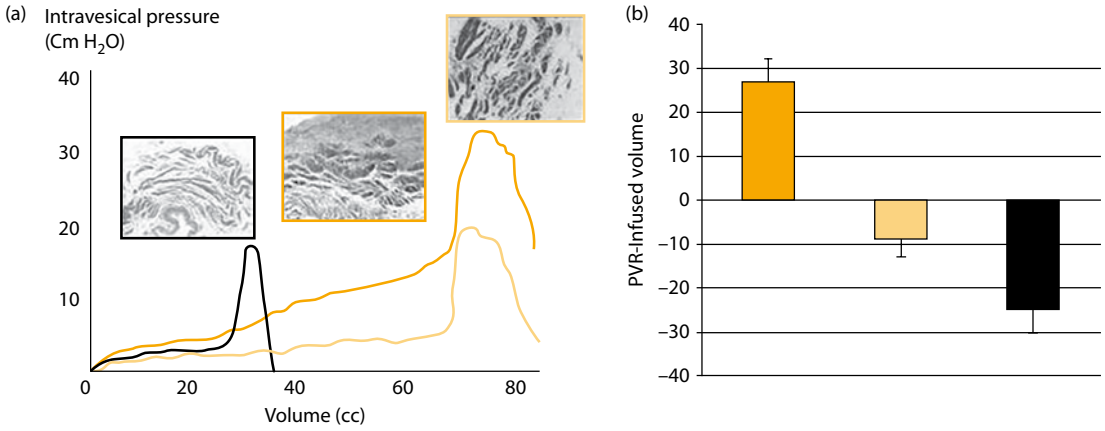

FIGURE 64.19 Experimental work demonstrates the relationship between a noncompliant bladder and postobstructive diuresis. (a) Following partial bladder outlet obstruction in rabbits, we performed videourodynamics free of any sedation 24 hours after placement of bladder and peritoneal catheters. For the sham control (▬), we recorded a normal slow fill cystometrogram (CMG) terminating in a voluntary void to completion. For decompensated bladders, we observed two populations of curves. In one group of bladders, compliance was preserved if expressed as ΔP/ΔV; however, the resting pressure just before voiding was higher (▬). However, for a second group of decompensated bladders, a noncompliant pattern was observed with a much higher resting pressure before void (▬). In each instance, we recorded an accurate postvoid residual with fluoroscopic confirmation. Note the increased deposition of extracellular matrix elements in the two decompensated bladders. (b) If one subtracts the infused volume from the postvoid residual, and exceeds zero, this is evidence of a diuresis that occurs during bladder filling. We observed the presence of a postobstructive diuresis only in those noncompliant decompensated bladders whose resting pressure before voiding exceeded 10 cm H_2O. (Adapted from Stein R et al. *J Urol* 2001;166(2):651–7.)

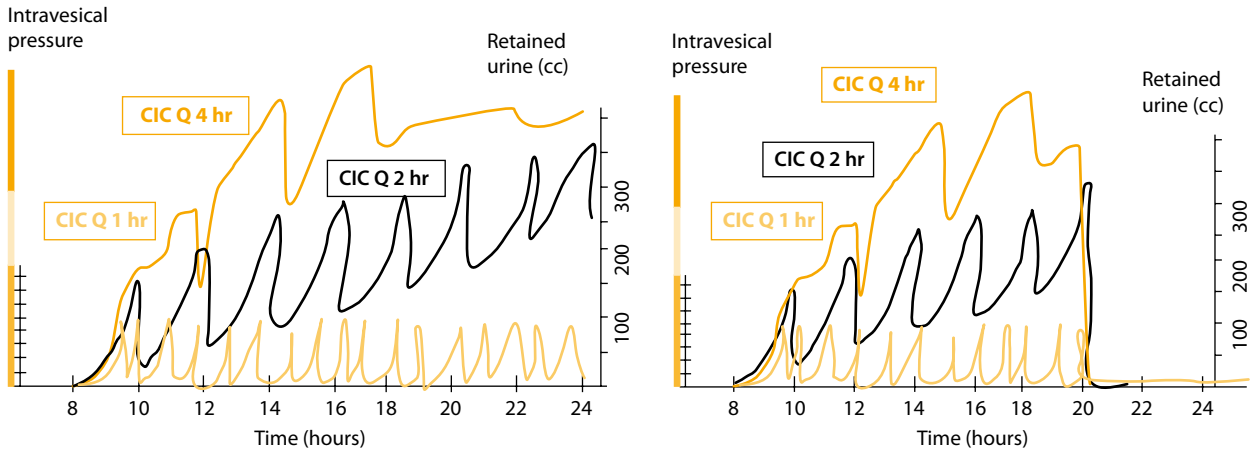

FIGURE 64.20 These two panels demonstrate the concepts of a safe pressure storage zone, and the role of overnight catheter drainage. As shown in both panels, maintaining a safe storage pressure (green zone on the left) for a patient with polyuria this severe is possible only with a regimen of CIC at 1-hour intervals. As CIC moves to 2-hour intervals, the daytime hours drift upward from the green to the yellow pressure zones as illustrated in the panel on the right. However, at 4-hour CIC intervals, the red zone of high intravesical pressures is reached during the waking hours, and prolonged exposures to high red zone pressures are maintained during the overnight hours. However, with overnight catheter drainage, the hours of exposure at high pressure at night are minimized. An additional benefit with this particular patient was that renal concentrating ability improved and the total volume produced per 24 hours dropped, making daytime dryness easier to attain and at lower intravesical pressures.

team as ESRD approaches. Boys undergoing transplantation with a poorly functioning bladder have higher complication rates and graft loss than those in whom lower urinary tract function has been optimized.[123,124] *We recommend videourodynamics assessment for any boy in whom transplantation is anticipated. This allows for determination of the volume for safe bladder storage pressure and assessment of whether CIC is required.* Videourodynamics studies may also reveal that high-grade reflux into the native ureters provides additional compliance to the system (Figure 64.17). For this reason, we rarely recommend nephrectomy. The principal indications for pretransplant native nephrectomy are the presence of severe polyuria or hypertension that is difficult to control. We have rarely witnessed new urinary tract infection into the native kidney following transplantation if infection was not common before the transplant. *If nephrectomy is indicated, consider preserving the ureters for catheterization, augmentation, or anastomosis to the transplanted kidney should problems arise within the transplanted ureter.*

If videourodynamics reveals that the bladder capacity must be expanded to provide safe storage pressures, ureteral augmentation is an option.[125] Very rarely, augmentation using a bowel segment may be necessary. In the past, dogma required that total bladder reconstruction, including augmentation if required, must occur before transplant. Our experience has been different. *We have been pleased with the results of transplantation to the vesicostomy in the unusual cases where low bladder volume and poor compliance resulted in lower tract diversion.*[126] Under these conditions, the transplant team should not hesitate to reimplant the transplant ureter into a diverted bladder that is draining via a vesicostomy.[127] With this approach, we have successfully postponed reconstruction with the associated CIC to an age-appropriate date and, in some cases, with the addition of overnight catheterization, avoided the need for augmentation altogether.

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CHAPTER 65

Prune Belly Syndrome

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INTRODUCTION

The classic definition of prune belly syndrome is the triad of bilateral cryptorchidism, deficiency of the abdominal wall musculature, and a dilated, dysmorphic urinary tract (Figure 65.1). The degree of involvement of the genitourinary system combined with the appearance of the abdominal wall engenders intense interest in the etiology, clinical features, and management of this developmental anomaly.

A rich history surrounds the clinical definition of prune belly syndrome (Table 65.1). In 1839, Frolich noted the abdominal wall "tumidity."[1] Parker, in 1895, recognized the essential elements of the syndrome, including a large flaccid abdominal wall with absent musculature, undescended testes, and a hypertrophied bladder and dilated renal collecting system without urethral obstruction.[2] William Osler is credited with giving the syndrome its name "prune belly" in 1901. Prune belly syndrome is, at present, the most widely accepted appellation.[3] Other popular synonyms—Eagle-Barrett syndrome, urethral obstruction malformation complex, the triad syndrome, abdominal muscle deficiency syndrome, and mesenchymal dysplasia syndrome—reflect the etiologic biases of the respective authors.[4–7]

Unfortunately, patients with prune belly syndrome can have many associated conditions that have a significant clinical impact. These include pulmonary hypoplasia, renal dysplasia/insufficiency, cardiac anomalies, lower extremity musculoskeletal malformations, imperforate anus, and intestinal malrotation/malfixation. These conditions impart a significant morbidity in prune belly patients and often influence urologic management. They have also been shown to be an important contributor to the decreased health-related quality of life in both children and their families with prune belly syndrome.[8]

A continued area of controversy in the management of prune belly syndrome is the role of surgical reconstruction. Prevention of urinary infection and preservation of renal function may be equally obtainable with observation.[9–12] Early series stressed the importance of relief of obstruction and stasis by high ureterostomies or catheter drainage. Indwelling catheter drainage often met with infectious complications with an additional 30% mortality reported in the first two years of life.[13,14] Later reports of successful early urinary reconstruction demonstrated both improved urinary drainage and radiologic configuration of the urinary tract. Long-term follow-up demonstrated stabilization of renal function.[6,15–18] However, with the development of improved prophylactic antibiotic therapy and utilization of advanced urodynamic equipment, the need for extensive tailoring of the urinary tract has been questioned. In fact, Woodhouse reported a normal serum creatinine in 27 patients with prune belly syndrome who had limited surgical intervention over a 29-year period.[19] Regardless, mindful of psychological and fertility considerations, current practice dictates an early surgical role in correction of the abdominal wall defect and the cryptorchid testes.[20–23] In fact, musculoskeletal reconstruction has been shown to be the factor with the largest positive impact on the patient quality of life.[24]

Further improvements in the treatment of prune belly syndrome include the application of prenatal diagnosis and intervention, dialysis, renal transplantation, and laparoscopic procedures. Transplantation offers hope to patients with poor renal function due to initial renal dysplasia or progressive chronic renal insufficiency despite appropriate urologic intervention. This chapter reviews proposed etiologies of the syndrome, associated malformations, and the spectrum of management of these patients.

SPECTRUM OF DISEASE

Prune belly syndrome represents a spectrum of disease. Classification systems based on the clinical spectrum have been formulated by numerous authors and all take into consideration initial and subsequent renal function.[6,23,25,26] The classifications have similar, clinically distinctive parameters to segregate the patients prognostically. The clinical classification of prune belly syndrome provides a framework for a more rational approach to overall management, which is determined on an individual basis.[27] Based on Woodard's classification, three major categories can be broadly defined (Table 65.2).

Category I patients exhibit the most severe form of the prune belly syndrome with pulmonary hypoplasia and severe renal dysplasia. Most patients in this category do not survive beyond the first few days of life. Stillborn births are often associated with oligohydramnios and the classic features of Potter's syndrome.[28,29] In this subset of patients with severe renal dysplasia, high urinary diversion is ineffective.[6] Initial normal serum creatinine progressively rises in spite of urinary diversion. These patients may also have complete urethral obstruction or atresia,

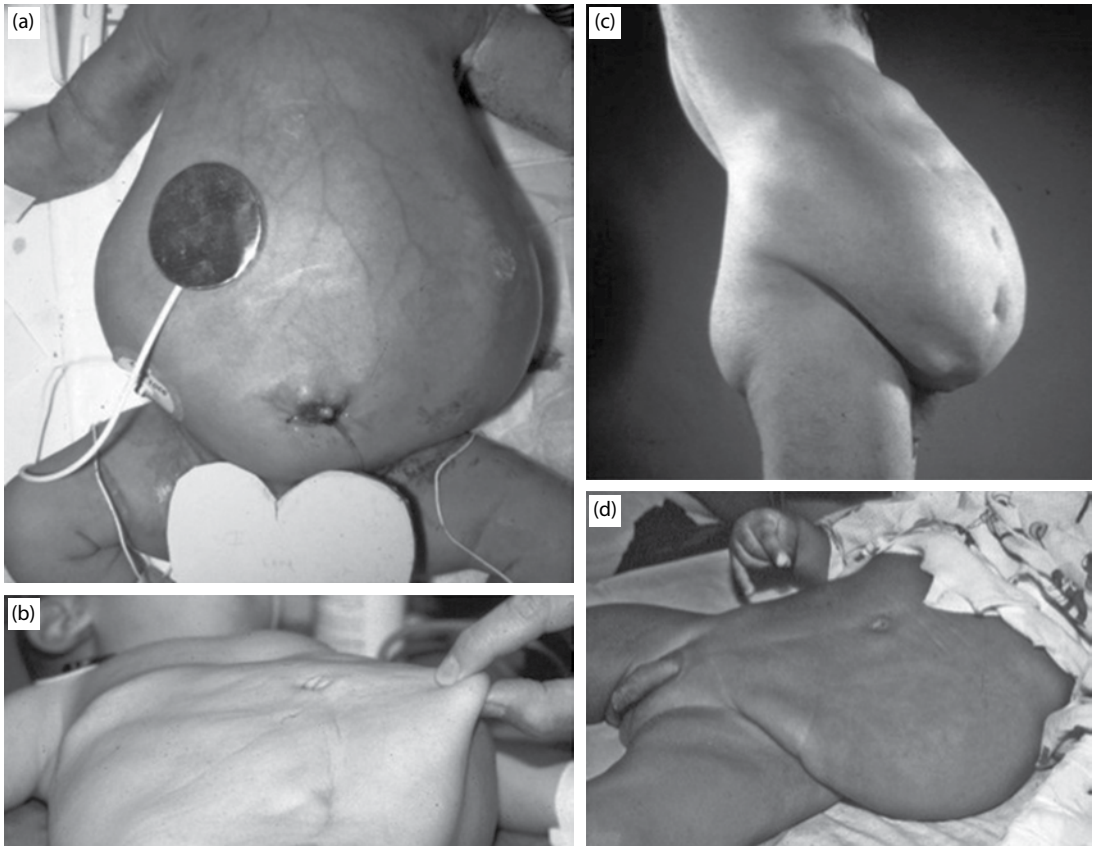

FIGURE 65.1 (a) A newborn with prune belly syndrome, urinary ascites, and pulmonary hypoplasia. Outline of the bowel is visible through the abdominal wall. (b) An infant with prune belly syndrome before comprehensive reconstruction. (c) An adult with prune belly syndrome exhibiting "pot belly" configuration. (d) A 4-year-old female child with hemiprune belly.

TABLE 65.1 History of prune belly syndrome

Year	Author	Discovery
1839	Frolich	Described abdominal wall abnormality
1895	Parker	Recognized all three components of the syndrome
1901	Osler	Coined the name prune belly syndrome
1903	Strumme	Proposed obstructive hypothesis
1961	Nunn and Stephens	Proposed theory of mesodermal arrest as an etiology of prune belly syndrome
1999	Thomas	First reported case of fertility in male with prune belly syndrome
2012	Hillman	First female patient to carry a pregnancy with prune belly syndrome

TABLE 65.2 Spectrum of prune belly syndrome

Category classification	Distinguishing characteristic
I	Oligohydramnios, pulmonary hypoplasia or pneumothorax. May have urethra obstruction or patent urachus and clubfoot
II	Typical external features. Uropathy and the full-blown syndrome but no immediate problem with survival. May have mild or unilateral renal dysplasia. May or may not develop urosepsis or gradual azotemia
III	External features may be mild or incomplete. Uropathy less severe. Stable renal function.

considered the "lethal variant" of the syndrome unless associated with a patent urachus.[30]

Category II includes those infants who do not have pulmonary hypoplasia but have significant involvement of the urinary tract. This can involve mild-to-severe renal dysplasia with potential azotemia and failure to thrive. The clinical course is one of either stabilization of renal function or progressive azotemia. Surgical intervention has been successfully performed to tailor the urinary tract to provide unimpeded drainage and decrease stasis. The impact of surgical intervention on long-term renal function remains debated and is a source of continued controversy.[13,18,31]

Category III patients with prune belly syndrome are associated with the external abdominal features and undescended testes but neither pulmonary nor renal function is severely impaired. They constitute the majority of patients with prune belly syndrome.[22,26] Although these infants may have severe dilatation of the urinary tract, they have stable renal function and usually do not require reconstructive urologic surgery.[23]

Prune belly morphology is not confined to the male gender. Females constitute about 3%–5% of recorded

cases.[16] The strict criterion of cryptorchidism effectively eliminates the syndrome in female patients, but the descriptive term "prune belly" still applies. There is a strong association with omphalocele and bladder outlet obstructive lesions in female patients with prune belly morphology.[32] In a review by Reinberg, 40% of female prune belly patients had anorectal anomalies and the perinatal mortality was 40%.[33] The term "pseudoprune" has been suggested to define females and males who do not have the complete triad of prune belly syndrome.[3] Hence, males with a lax abdominal wall but without undescended testes or without a dilated urinary tract and all females are considered pseudoprunes. The principles of management are essentially the same as in the classic syndrome patient. The underlying uropathy and clinical course in patients with pseudoprune belly syndrome are unpredictable and in one series 63% went on to renal failure.[34]

INCIDENCE AND INHERITANCE

The incidence of prune belly syndrome is 1/29,000 to 1/40,000 live births.[27,35] A variety of inheritance patterns have been associated with prune belly syndrome. The majority of cases are sporadic and have a normal karyotype.[23,35] Prune belly syndrome has been reported in male siblings, cousins, and twins.[36–40] However, the majority of twins are discordant for prune belly syndrome, which argues against a simple chromosomal etiology. Ives noted 11 pairs of twins discordant for the syndrome, 6 were monozygous and 5 were of unknown zygosity. Of the 250 cases of prune belly syndrome reviewed, 4% (11 cases) occurred in twins compared to the 1.25% incidence of twins in the general population. Unequal division of mesodermal cells during primitive streak formation may explain the discordant monozygotic twinning phenomenon.[7]

Williams was one of the first to suggest that prune belly syndrome was due to a sex-linked recessive trait, accounting for the male predominance of the syndrome, its occurrence in male siblings and concordant twins, and its association with Turner's syndrome.[9,41] However, the presence of prune belly syndrome in three females with documented 46 XX karyotype contradicts this pattern of inheritance.[16]

Autosomal dominant and autosomal recessive inheritance have also been reported.[36,42,43] It is difficult to make an association with single-gene inheritance at this time because of male predominance, lack of pedigrees with consanguinity, and limited number of offspring due to associated infertility.[35] Riccardi and Grum suggested a two-step autosomal dominant mutation with sex-limited expression that partially mimics X-linkage.[39] This genetic inheritance pattern would explain male predominance, as well as the small number of affected family members.

Specific chromosomal abnormalities are rare. Several cases of hepatic nuclear factor 1-beta (HNF1β) mutations have been reported—a gene thought to play a role in prostatic and ureteral development.[44] However, genetic analysis of 32 prune belly syndrome patients revealed only 1 case of an HNF1β mutation.[45] Therefore, the genetic basis of this disease remains largely unknown. Trisomies 18 and 21 have been demonstrated in prune belly syndrome.[46–49] Trisomy 18 is also associated with other genitourinary abnormalities including renal dysplasia and hypoplasia, horseshoe kidney, duplication anomalies, and persistent nodular renal blastema.[50] A cause and effect relationship is only speculative. A careful analysis of incidence and birth rates suggests that these are independent events, occurring together by chance alone.[51]

An association with Turners syndrome suggests that the gene responsible for the syndrome may be located on the X chromosome and is recessively transmitted. However, it likely represents the occurrence of the prune belly phenotype in the female as a result of other causes of abdominal distention such as impaired lymphatic development with chylous ascites.[4,36,41] Although mosaicism for a monosome of chromosome number 16 in two male siblings with prune belly syndrome has been documented, its importance etiologically cannot be determined.[52] An extracentric chromosomal fragment was reported in association with prune belly syndrome.[53] However, the same aberration was present in two phenotypically normal male family members.

Prune belly is occasionally described in association with other syndromes, chromosomal aberrations, and conditions. Perlman syndrome, Beckwith-Wiedemann syndrome, VACTERL association, Pfeiffer syndrome type 3, and megacystis–microcolon–intestinal hypoperistalsis syndrome have been described in patients with prune belly syndrome, suggesting the possibility of a common pathogenesis.[54–57]

EMBRYOGENESIS

Three major theories have been proposed to explain the clinical features of the prune belly syndrome. As with most theories, none completely explains the entire constellation of findings in the syndrome, and all are marred by conjecture and speculation.

Fetal Outlet Obstruction

In 1903, Strumme proposed that prune belly syndrome was the final expression of an obstructive urologic lesion producing significant backpressure at a critical time during development. The dilation of the urinary tract and secondary pressure atrophy of the abdominal wall produced the clinical features common to prune belly syndrome (Figure 65.2).[58] Subsequent clinical reviews reflected this belief and called attention to the need to alleviate the obstructing lesions commonly found in the posterior urethra.[14,25,30,59] Improved methods of radiographic diagnosis of obstruction with the voiding cystourethrogram, postmortem anatomic en-bloc dissections, and the application of urodynamics cast doubt on the anatomic presence of obstruction.[5,9,10,60] Clinical reports found evidence of an obstructing lesion in 10%–20% of patients contrasted with up to 80% in earlier series.[12,59] It has been proposed that those infants with the most severe manifestations of the syndrome have the "lethal variant" (an anatomic obstructing lesion) leading to pulmonary hypoplasia, renal dysplasia, and death.[30] This distinction is particularly important when studying the theories of pathogenesis,

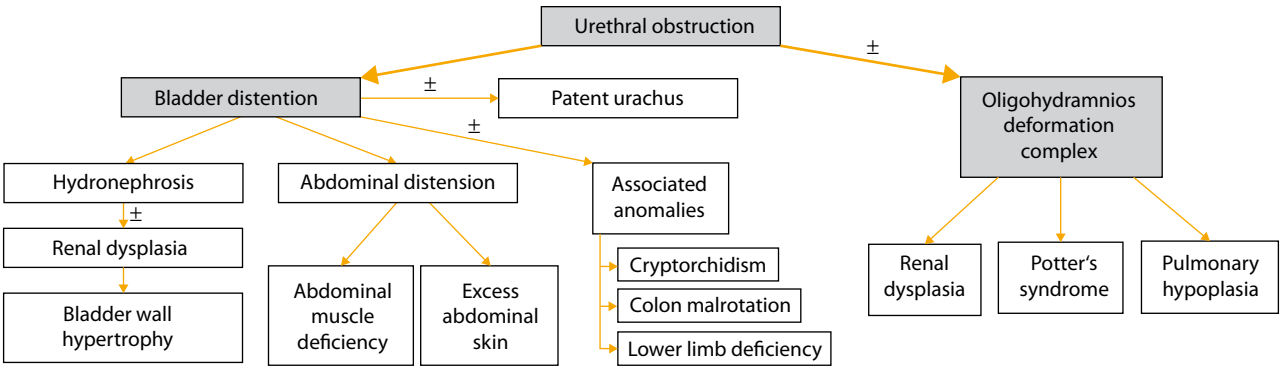

FIGURE 65.2 Urethral obstruction, whether anatomic or functional, is a proposed etiology of prune belly syndrome and its associated anomalies.

as most articles that indicate obstruction as the primary cause are based on autopsy information.[25,61–64]

The source of the obstruction may be true areas of stenosis, atresia, valves, or pinpoint diaphragms at the junction of the posterior and membranous urethra. Recent theories have suggested a "functional obstruction" present in utero, secondary to prostatic hypoplasia, as the specific etiology of the syndrome. This "obstruction" is thought to be the result of conformational changes in the prostatic urethra during voiding, creating a valve-like mechanism.[50,61] Haploinsufficiency of HNF1-β may be causally related to the production of the prune belly syndrome phenotype through a mechanism of prostatic and ureteral hypoplasia that results in severe obstructive uropathy with urinary tract and abdominal distension.[44] Another etiology suggested is a transient obstruction at the junction of the glandular and penile urethra. This was based on evidence of anterior urethral dilatation in patients with prune belly syndrome measured on radiographs from a voiding cystourethrogram. Comparisons were made with children with urinary tract infections and children with posterior urethral valves.[65] This theory is supported by the high incidence of megalourethra seen with prune belly syndrome.[66,67]

The obstructive theory contends that the abdominal wall findings are secondary to the pressure effects of the distended bladder on the developing myotomes of the abdominal wall. The muscles directly over the bladder: transversus abdominis, obliques and lower rectus are most severely affected, supporting this theory. However, histological studies and electron microscopy of the abdominal wall do not demonstrate a pattern of atrophy, but one of developmental arrest.[68–70] In addition, the absence histologically of any aponeurotic layer of the affected muscles opposes an atrophic cause.[70]

Evidence from prenatal ultrasound in patients with prune belly syndrome and other disease processes associated with the prune belly phenotype, suggests that the abdominal wall laxity is due to abdominal distention. A transient, ascitic distention accounts for patients with the syndrome who lack evidence of urethral obstruction.[4,71–74] One study indicates a heterozygous mutation in ACTA2 R179H that was present in a normal karyotype newborn with prune belly sequence without evidence of mechanical bladder outlet obstruction.[75] Urinary ascites has been demonstrated in utero in patients with prune belly syndrome. The urine is theorized to leak into the abdomen via the distended urinary tract and spontaneously reabsorbs at the end of gestation, which explains its clinical absence at birth.[72,74,76–78] Other causes of in utero abdominal wall distention and the prune belly phenotype include: nonimmune ascites, intestinal duplication, posterior urethral valves, amniotic band syndrome, visceromeglia, polycystic kidneys, impaired lymphatic drainage in Turner's syndrome, giant liver cyst, and cystic adenomatoid malformation of the lung.[4,73,79–81] The "urethral obstruction malformation complex" is applied to the theory of fetal outlet obstruction as the etiology of prune belly syndrome. The timing and severity of the obstructive phenomena are critical. The distension of the urinary tract at 13–15 weeks of gestation could produce the degenerative changes in the abdominal wall and urinary tract, preventing gut rotation and prostatic development.[82] This broader application of Strumme's original hypothesis fails to explain (1) the lack of hypertrophy and hyperplasia present in the obstructed urinary tract, (2) the replacement of smooth and skeletal muscle by fibrous and collagenous tissue, (3) normal or low intravesical pressures assessed urodynamically, (4) absent obstruction but presence of renal dysgenesis in the majority of patients, (5) other causes of in utero outlet obstruction not associated with abdominal wall laxity, and (6) the excessively high incidence of cryptorchid testes. All these factors are common in prune belly syndrome and cannot be completely explained on the basis of obstruction alone.[5,9,60,83,84]

Theory of Mesodermal Arrest

The theory of mesodermal arrest as an etiology of prune belly syndrome is based on an embryological aberration of mesenchymal development (Figure 65.3).[5] Urinary tract obstruction occurs in some patients as a consequence of the primary defect and may increase the pathological severity.[82] Stephens has proposed the genitourinary tract, the testes, and the abdominal wall would be vulnerable to a mesodermal defect occurring between the sixth and tenth weeks of gestation.[85] A noxious insult occurring when the lateral plate mesoderm has already extended to the midline, with failure of myoblast differentiation and migration ventrally and caudally, would explain the abdominal wall findings. At the same time, the urinary tract is developing from the

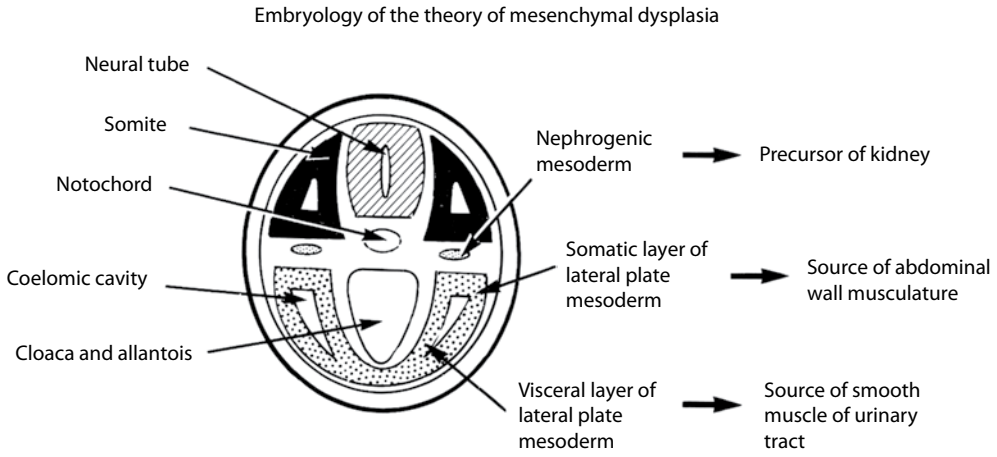

FIGURE 65.3 Cross section of a fetus at 6–10 weeks of gestation. An embryologic insult to both layers of the lateral plate mesoderm and the nephrogenic mesoderm could explain the majority of findings seen in the prune belly syndrome.

mesoderm of the visceral layer of the lateral plate mesoderm. The same insult would impair differentiation of the mesoderm that forms the smooth muscle of the urinary tract, resulting in the characteristic dilatation and dysmorphic features common to the syndrome. The kidneys are concurrently differentiating from the para-axial mesoderm. A defect in induction by the ureteral bud or an abnormality in the metanephric blastema, with or without subsequent urinary tract obstruction, would account for the renal dysplasia commonly associated with prune belly syndrome.[27,64,85]

Some authors have suggested that this insult must occur early in the third week of embryogenesis, at the primitive streak stage of development. At the division of the embryonic disk, an unequal distribution of mesoderm could explain the discordant occurrence in monozygotic twins.[7] This localized defect in mesodermal development would also explain the abnormalities seen in the prostate, urethra, and in testicular descent. According to this theory, the prostatic hypoplasia with poor glandular development, and abnormalities in the mesenchyme of the testicular gubernaculum, result in unresponsiveness of these tissues to hormonal stimulation.[64,86–88] This unresponsiveness of the gubernaculum to hormonal stimulation, the diminished intra-abdominal pressure, and potential mechanical obstruction by an enlarged bladder, all contribute to the maldescent of the testes in the prune belly syndrome.

The mesodermal arrest theory is further supported by histologic findings in the abdominal wall, the urinary tract, and the male genital tract. The abundance of fibrous tissue, collagen and connective tissue, in association with sparse smooth muscle throughout the urinary tract, indicates an inherent problem with mesodermal differentiation. Bladder outlet obstruction, as seen in posterior urethral valves, results in hypertrophy and hyperplasia in the urinary tract with normally developed seminal ducts, seminal vesicles, and prostate glands that are proximal to the obstruction. These features are noticeably absent in the prune belly syndrome.[5,60,68,85,86,89] The absence of anatomic obstruction in the majority of patients and the demonstration of urodynamically unobstructed urinary tracts supports this theory. It also provides an adequate explanation for the high association with megalourethra.[5,66,90]

Nevertheless, the mesodermal arrest theory does not explain the male predominance of the syndrome. It also fails to explain the myriad associated anomalies and the presence of the abdominal wall abnormalities with a normal urinary tract. In addition, obstructive urethra lesions, whether anatomic or functional, are associated with the syndrome. The development of an animal model, with all the features of the syndrome, due to urethral ligation has been reported.[50,61,90]

The Yolk Sac Theory

Stephens proposed an additional theory to explain the features of the prune belly syndrome. There is no genetic evidence to support this theory. Nevertheless, the premise is based on an error in embryogenesis of the yolk sac and allantois. Inherent in this theory is the contention that the bladder and prostatic urethra are derived from the allantois to a greater degree than customarily accepted. If an abnormally large amount of the yolk sac is retained inside the embryo, due to overgrowth of the lateral folds of the discord embryo, it could affect the development of the abdominal wall resulting in the prune belly phenotype. A critical aspect of this theory is the over development of the allantoic diverticulum. This structure grows out from the yolk sac contiguous with the body stalk. If it becomes excessively large due to the oversized intra-abdominal yolk sac, it would become incorporated into the urinary tract as the redundant enlarged urachus, bladder, and prostatic urethra which characterizes the syndrome.[70,85] Unfortunately, this theory does not explain the errors in development of the upper urinary tract or male genital tract.

CLINICAL FEATURES OF THE PRUNE BELLY SYNDROME

Extragenitourinary Manifestations

Associated Anomalies

Abnormalities of other organ systems result in long-term morbidity for as many as 75% of patients with prune belly

TABLE 65.3 Extragenitourinary abnormalities in prune belly syndrome

Organ system	Frequency (%)	Manifestations
Cardiopulmonary	49	Pulmonary hypoplasia Pneumothorax Pneumomediastinum Lobar atelectasis Pneumonia Chronic bronchitis Patent ductus arteriosus Atrial septal defect Ventricular septal defect Tetralogy of Fallot
Orthopedic	65	Congenital dislocation of hips Chest wall deformity: Pectus excavatum/ carinatum Scoliosis Genu valgum Talipes equinovarus Severe leg maldevelopment: Arthrogryposis
Gastrointestinal	63	Malrotation Intestinal atresia Intestinal stenosis Volvulus Anorectal agenesis Imperforate anus Omphalocele Gastroschisis Hepatobiliary anomalies Acquired megacolon

syndrome (Table 65.3).[91] Growth was impaired in 32% of surviving patients in one large series and was poorly correlated with renal function. This impairment was most manifest in the first year of life with subsequent stabilization but incomplete catch-up growth.[91] Developmental delay was reported in 43% of the most contemporary cohort.[24]

The non-urological associated anomalies in patients with prune belly syndrome are a major source of morbidity and mortality. Care of these patients requires close cooperation with all caregivers. The urological manifestations of prune belly syndrome rarely require emergent treatment.

Cardiopulmonary

Cardiopulmonary anomalies have been reported in up to 49% of patients with prune belly syndrome (see Table 65.3).[24] Patent ductus arteriosus, atrial and ventricular septal defects, and tetralogy of Fallot occur with increased frequency in prune belly syndrome.[92,93] The severity of the cardiac involvement will dictate initial care of the infant, as the urologic anomalies rarely demand immediate treatment.

Pulmonary and respiratory difficulties pervade the lives of these patients from birth to adulthood. Severe pulmonary hypoplasia, with associated oligohydramnios and renal dysplasia, is fatal. Initial prognosis is dependent upon pulmonary development. A review of most series demonstrates that approximately 20% of newborns will die in the perinatal period as a consequence of pulmonary complications.[18,20,21] Of those that survive the newborn period, clinically significant pulmonary problems were noted in 55% of patients.[91] Pneumothorax and pneumomediastinum may be present at birth, with or without pulmonary hypoplasia and an early chest x-ray is advised. Chest wall deformities and abdominal muscle deficiency impair mechanical ventilation, which results in a ventilatory limitation and a high incidence of lobar atelectasis and pneumonia.[94,95] Chronic bronchitis and the development of respiratory insufficiency following upper respiratory infections or anesthetics are well recognized, and appropriate pulmonary support must be provided.[91,94]

Gastrointestinal

Gastrointestinal anomalies are present in up to 63% of patients with prune belly syndrome (see Table 65.3).[24] These anomalies are commonly recognized in the postnatal period. The majority of anomalies such as malrotation, atresia, stenosis, and volvulus are due to persistence of the wide embryonic mesentery, without fixation to the posterior abdominal wall.[96] This same suspension abnormality allows the spleen to wander freely in the abdominal cavity and acute splenic torsion has been reported on two occasions.[97] It has been recommended that all patients with prune belly syndrome have radiographic assessment of their alimentary tract.[96] Anorectal agenesis, imperforate anus, omphalocele, pouch colon, and gastroschisis have been reported in association with prune belly syndrome.[96,98–102] Chronic constipation is a frequent problem with these children, attributed to a decrease in abdominal wall pressure aiding evacuation. Acquired megacolon can result. Chronic constipation requires continuous attention with dietary and cathartic intervention.[27,91]

Orthopedic

Orthopedic-related problems in prune belly syndrome are present in up to 65% of cases (see Table 65.3).[24,103] In most series, musculoskeletal anomalies predominate in frequency of occurrence with congenital dislocation of the hips, clubfoot, and/or scoliosis the most frequent findings.[100,104] Congenital dislocation of the hip requires early institution of treatment and may be resistant to conventional therapy.[103] Lateral dimples of the elbows and knees are the mildest manifestation of the compression effect of intrauterine oligohydramnios (Figure 65.4). More severe deformities, attributed to oligohydramnios and intrauterine compression, are recognized usually at autopsy as lower limb deficiencies and arthrogryposis.[4,105] Talipes equinovarus, polydactyly, syndactyly, and torticollis have been reported.[10,64] Pectus carinatum and pectus excavatum deformities are frequently present. Scoliosis is the most common spinal deformity.[104] In one instance, scoliosis was associated with thoracic segmental insensibility.[106] As prognosis improves in these patients, orthopedic interventions will play a greater role in management.

Abdominal Wall

The wrinkled, floppy abdominal wall that characterizes the syndrome results from a deficiency of the underlying

FIGURE 65.4 Lateral dimple of the knee in this infant with prune belly syndrome is a mild manifestation of the compression effects of intrauterine oligohydramnios.

musculature. The functionally impaired abdominal wall can result in significant morbidity. Affected infants are unable to sit up directly from the supine position, delaying the onset of walking.[3] The lack of mechanical assistance from the abdominal wall contributes to difficulties with respiratory infections and chronic constipation.[91] In addition, patients suffer long-term psychosocial effects of poor body image.[22,23]

Autopsy studies have shown that the muscles most severely affected are those ventral and lateral in location. The epaxial and hypaxial trunk muscles develop normally. The order of severity of involvement from most to least is: transversus abdominis, rectus abdominis below the umbilicus, internal oblique, external oblique and rectus abdominis above the umbilicus (Figure 65.5).[2,14] There is cephalic displacement of the umbilicus due to unopposed contraction of the upper rectus abdominis muscle. The diminished muscle mass, if severe, allows one to observe bowel peristalsis and easily palpate the abdominal organs and kidneys. Because the muscular deficiency may not be symmetric, a more dominant flank bulge on one side of the abdomen is often present and coincides with the dilated distal ureter (Figure 65.6).

Electromyographic studies of the abdominal wall have confirmed the anatomic findings. The lower midline musculature demonstrates the least amount of electrical activity. Recruitment of voluntary motor units is greatest in the upper lateral musculature.[107]

Autopsy studies of the abdominal wall have demonstrated normal segmental nerve distribution and normal blood supply.[64,70] The distribution of muscle fibers is haphazard. In more severe cases, the entire thickness of the abdominal wall consists of skin, connective tissue, superficial fascia, and peritoneum (Figure 65.7). In the infant there is no aponeurotic layer that might represent atrophied muscle.[9] Fortunately, the poorly developed abdominal wall heals well despite the muscular layer deficiencies.

Microscopic examination demonstrates fat interdigitating with muscle fibers. These fibers have been characterized as hypoplastic, atrophic, and hypertrophic adding further confusion to an apparent etiology.[68,108] Others have found the muscle cells to be clear and normal in appearance and

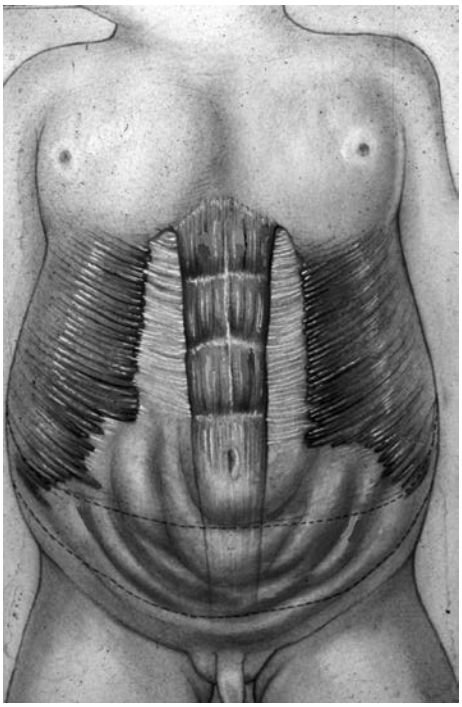

FIGURE 65.5 Abdominal wall deficiencies in prune belly syndrome. The epaxial and hypaxial trunk muscles develop normally. The order of severity of involvement from most to least involved is: transversus abdominis, rectus abdominis below the umbilicus, internal oblique, external oblique, and rectus abdominis above the umbilicus.

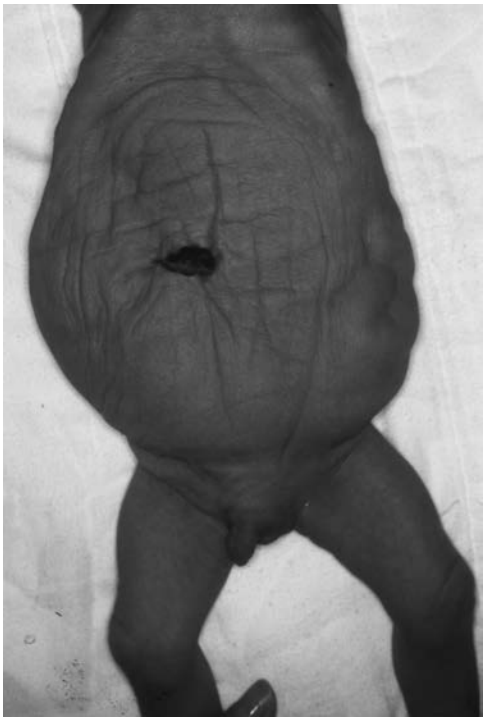

FIGURE 65.6 A newborn with prune belly syndrome. The classic abdominal deficiency exists, with a dilated, tortuous, and easily palpable left ureter exhibited along the left flank.

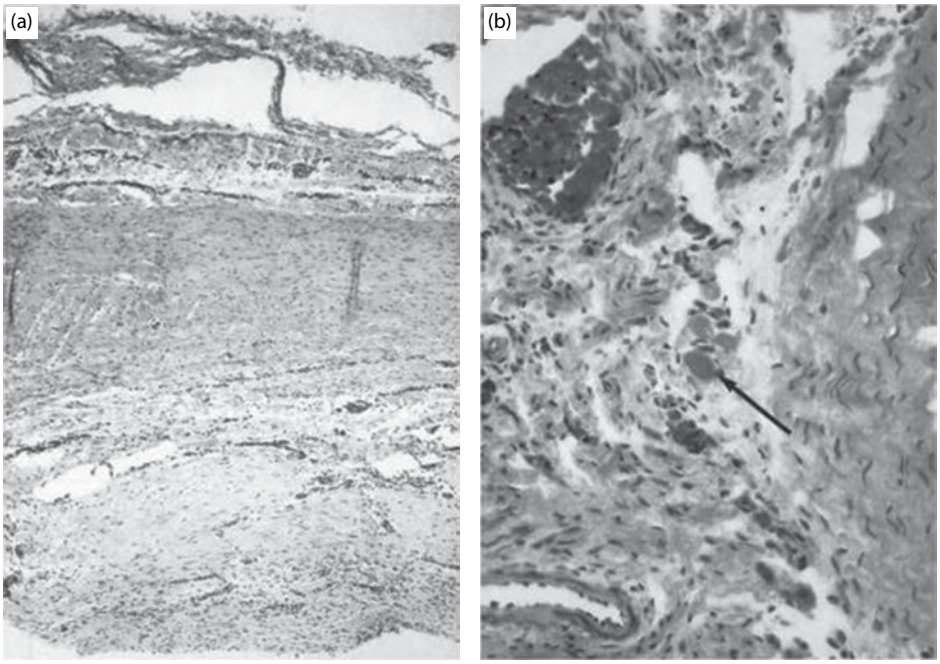

FIGURE 65.7 (a) A cross section of the abdominal wall of an infant with prune belly syndrome. Note the scant and haphazard arrangement of muscle fibers. (b) A high power view of abdominal wall composed largely of collagen and fibrous tissue. The arrow points to scant skeletal muscle fibers.

at times associated with myotubular embryonic cells similar to that seen in the fetus of about 10 weeks gestation.[69,70] Ultrastructural abnormalities, demonstrated by electron microscopy, include loss of coherence and orientation of the Z bands, mitochondrial disruption, and clumping of glycogen granules. These changes are nonspecific, but are consistent with hypoplastic histologic changes.[68]

Genitourinary Manifestations

Kidneys

Renal dysplasia and hydronephrosis are the common denominators of the upper urinary tract in prune belly syndrome. Both grossly and radiographically, cystic dilatation of the calyces and renal pelvis is present. Infundibular narrowing without obstruction and occasional ureteropelvic junction obstruction may be evident.[18] Wide variations may exist in individual renal unit appearance, function, location, and rotation (Figure 65.8).[64]

Prognosis is directly related to renal function and the degree of renal dysplasia. Stephens proposed pathogenic mechanisms to explain the development of renal dysplasia. These include (1) defects of the ureteric bud or its branches, (2) qualitative or quantitative deficiencies of the nephrogenic mesenchyme, and (3) vascular ischemic insults with resultant ureteric obstruction and renal cystic dysplasia. He suggested that the renal dysplasia of the prune belly syndrome is due to a combination of a ureteric bud and metanephric defect.[70]

The most severe degree of renal dysplasia is recognized from autopsy studies and associated with both Potters type II and IV renal cystic changes.[64,83] These patients have associated distal outlet obstruction (urethral atresia) with a non-patent urachus, and they are usually stillborn. The kidneys are small, with disorganizational features of dysplasia and are most likely injured prior to significant nephron formation at the stage of ampullary development.[25]

In contrast, some patients have hydronephrosis but adequate renal function. The degree of hydronephrosis may not correlate with the ureteral dilatation or the abdominal wall deficiency. The renal parenchyma is often well preserved despite a grossly abnormal drainage system. Urinary infection rather than obstruction represents the greatest threat to the renal parenchyma. The dilatation is attributed to the mesenchymal defect and deficient smooth muscle, not to obstruction. Consequently, some resolution in the degree of dilatation can occur spontaneously in follow-up.

Ureters

The ureters are elongated, tortuous, and dilated forming the radiographic hallmark of the syndrome (Figure 65.9).[109] The lower one third of the ureter is more profoundly affected than the proximal portion and occupies the flared out flanks of the abdomen. Although fluoroscopic studies demonstrate ineffective peristalsis over its entire length, true obstructive lesions of the ureter are the exception. However, pleat-like valves at the ureterovesical junction (UVJ) have been documented in two cases.[110]

Vesicoureteral reflux is seen in up to 85% of patients. The conventional system of grading reflux is difficult to apply due to the dysmorphic features of the ureter, renal pelvis, and calyces.[21]

Histologic examination of the ureter demonstrates a profound alteration in the content and architecture of the ureteral wall. Prune belly ureters lack the hypertrophy and hyperplasia of the smooth muscle cells seen in dilated ureters due to obstruction or vesicoureteral. A diffuse increase in the connective tissue with replacement of the smooth

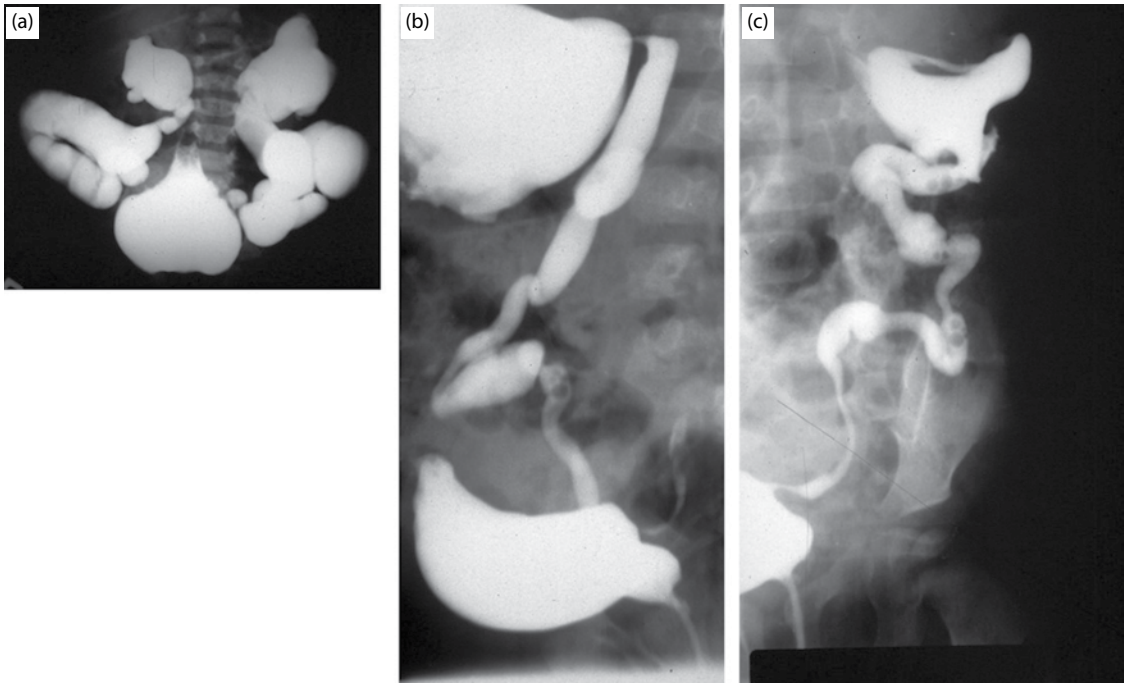

FIGURE 65.8 (a) Retrograde cystogram demonstrates dilated, tortuous, refluxing ureters; enlarged, floppy renal pelvis; and distended bladder, with urachal remnant. (b) Retrograde cystogram demonstrates vesicoureteral reflux into a dilated dysmorphic ureter. Renal pelvis indicative of pseudoureteropelvic junction obstruction. (c) Same patient as (b) with entire left ureter and renal pelvis visualization.

FIGURE 65.9 Voiding cystourethrogram of a 1-year-old child with prune belly syndrome exhibiting the classic elongates, tortuous, and dilated ureter representing one of the radiographic hallmarks of the syndrome. The large, distended bladder is thick walled. (Courtesy of George W Kaplan, MD.)

muscle is present. The ratio of collagen-to-smooth muscle, especially in refluxing ureters, is markedly elevated.[111] There is no differentiation into longitudinal and circular muscle layers. The patchy distribution of smooth muscle is present in both the dilated and narrowed ureteral segments. The upper ureter has more smooth muscle cells than the lower portion.[5,84] A marked decrease in the number of nerve plexuses, with degeneration of non-myelinated Schwann fibers, has been reported. This may contribute to the poor ureteral peristalsis even after corrective surgery.[91] Ultrastructural examination of the smooth muscle cells of the ureter reveals a decrease in the number of thick and thin myofilaments, which contributes to poor muscle cell performance.[84,112] The histologic and pathologic features are important to remember during genitourinary reconstructive efforts. The upper ureter is potentially best suited for definitive reconstruction and its future should not be risked by using it for temporary cutaneous diversion. The dilatation and ineffective peristalsis of the ureters result in urinary stasis and a heightened risk of infection.

Bladder

The bladder is thick walled and grossly enlarged and trabeculations are usually absent (Figure 65.10). The normal bladder contour is deviated by a pseudodiverticulum which consists of the urachal remnant giving the bladder an hour-glass configuration. A patent urachus may be present, especially in association with urethral atresia or microurethra. The trigone is splayed and the ureteric orifices are located laterally which explains the common association with vesicoureteral reflux.[70] The bladder neck is characteristically quite wide at its junction with the

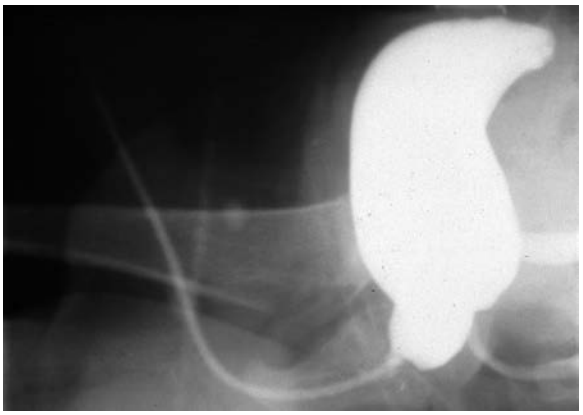

FIGURE 65.10 Voiding cystourethrogram details the grossly enlarged, but non-trabeculated bladder. The bladder neck is widely patent, with hypoplastic urethra.

FIGURE 65.11 Voiding cystourethrogram of a 1-year-old child demonstrating the classic radiographic appearance of the posterior urethra in prune belly syndrome. The open bladder neck and dilated prostatic/posterior urethra is evident. No urethral obstruction is present. (Courtesy of George W Kaplan, MD.)

prostatic urethra. Histologic evaluation of the bladder demonstrates an alteration in the ratio of connective tissue to smooth muscle. The extent of involvement is less than the ureter, and smooth muscle hypertrophy can be present.[64,113] The increased bladder thickness is largely due to fibrocytes and collagen. The anatomic innervation of the bladder is normal. No abnormality in the distribution of ganglion cells is present.[5,10] One study indicates an increase in alpha 1a-adrenoceptor immunostaining intensity in the detrusor muscle. In bladder outlet obstruction these receptors are up or down regulated.[114] In addition, muscarinic acetylcholine receptor M3 (CHRM3) (1q41–q44) homozygous frameshift mutation in familial congenital bladder malformation has been associated with a prune belly-like syndrome.[115]

The bladder in prune belly syndrome has efficient low-pressure storage and good compliance. However, its ability to empty is compromised by vesicoureteral reflux and poor contractility. Urodynamic assessment of the bladder has demonstrated normal balanced voiding in some patients regardless of the gross anatomic and radiologic features.[5] Three distinct patterns of voiding have been observed; normal, prolonged voiding with a low peak, and an intermittent pattern. The voiding pattern did not correlate with residual urine volume.[116] Maximum urinary flow rates and voiding pressures can be within normal limits for age. The filling phase of the cystometrogram is shifted to the right, with a markedly delayed first sensation to void. Bladder instability with uninhibited contractions is infrequent and usually not the explanation for urinary incontinence.[9,116,117] In those patients with unbalanced voiding manifested by urinary incontinence, an increase in residual urine with a decreased flow rate may be noted. Changes in voiding efficiency are not unusual and mandate the need for regular urodynamic assessment. Surgical intervention or intermittent self-catheterization may be necessary. Two cases of nephrogenic adenoma have been reported which initially presented with gross hematuria.[118,119]

Prostate and Posterior Urethra

The radiographic appearance of the prostatic urethra is quite distinctive. The bladder neck is open and the posterior urethra is dilated, elongated, and tapered at the membranous urethra (Figures 65.10 and 65.11). The anterior wall of the prostate is shorter than the posterior wall. It frequently has a localized sacculation, which represents a utricular diverticulum. Reflux into the vas deferens may be present and the verumontanum is small or absent. True obstructive lesions at the junction of the prostate and membranous urethra have been described in 20% of infants, usually those with the worst prognosis. These obstructions have been described as stenosis, true valves, atresia, diaphragms, and diverticula.[25,59,64,120] A kinking of the prostatic urethra during voiding, as a result of asymmetry of its anterior and posterior walls, has been suggested as a functional obstruction in prune belly syndrome. Stephens assigned a type IV valve classification to these lesions.[61,70]

Lack of development of the epithelial portion of the prostate is a constant component of the syndrome. When compared to normal children and children with posterior urethral valves, patients with prune belly syndrome have either absent or sparsely distributed prostatic epithelial glands.[5,85,86] The prostatic hypoplasia results from an inability of the urogenital mesenchyme to induce epithelial differentiation.[86] Prostatic hypoplasia is one of the etiologies of infertility in this syndrome.[121]

Accessory Male Sexual Organs

As with the other mesenchyme-derived genitourinary organs in the prune belly syndrome, abnormalities of the epididymis, seminal vesicles, and vas deferens have been noted. Autopsy findings have noted lack of continuity between the ductuli efferentes and rete testis. The body of the epididymis is frequently detached from the testes; a common finding with abdominal undescended testes. The vas deferens is abnormally thickened and may drain ectopically.[122] The seminal vesicles may be dilated with diverticular formation but usually are atretic or absent, which may be a diagnostic feature of prune belly syndrome.[85] All of these findings have significance in regards to the known infertility associated with prune belly syndrome.[70]

FIGURE 65.12 A newborn with prune belly syndrome with evidence of megalourethra and penoscrotal transposition.

Anterior Urethra

The recognized abnormalities of the anterior urethra in prune belly syndrome range from urethral atresia to fusiform megalourethra (Figure 65.12). Surviving patients with urethral atresia or microurethra have a patent urachus. It is possible that the microurethra is normally formed but unused and can be progressively dilated to a functional caliber.[123]

Bulbous urethral dilatation was evident in 68% of patients with prune belly syndrome.[66] Two of these patients had a fusiform megalourethra. Comparative measurements of anterior urethral diameters in patients with prune belly syndrome and normal patients, have confirmed a dilated anterior urethra in prune belly syndrome patients (Figure 65.13).[124] A transient obstruction during fetal development at the junction of the glandular and penile urethra may explain this common radiographic finding, as well as the known association of prune belly syndrome with megalourethra.[67]

Both types of megalourethra—scaphoid and fusiform—are associated with prune belly syndrome. The fusiform megalourethra, accompanied by deficient corpora cavernosa, is a more severe defect frequently associated with renal dysplasia and lethal anomalies. Scaphoid megalourethra is characterized as a deficiency of the corpus spongiosum with normal glans and fossa navicularis. In a series of 26 patients with this anomaly, 10 had prune belly syndrome.[125] The mesenchymal developmental arrest that accounts for the major features of the syndrome may also explain the urethral malformations.[66]

Testis

Bilateral cryptorchidism is an essential component of the prune belly syndrome. In the majority of patients the testes are intra-abdominal, overlying the ectatic ureters at the pelvic inlet. The epididymal abnormalities associated with abdominal undescended testis are present.[1] The intra-abdominal position of the testes predisposes these patients to increased risk of malignant degeneration of 30–50 times that of a normally descended testes.[126] At least three documented cases of testis tumor in prune belly syndrome have been reported, one of which was retroperitoneal.[3,127,128]

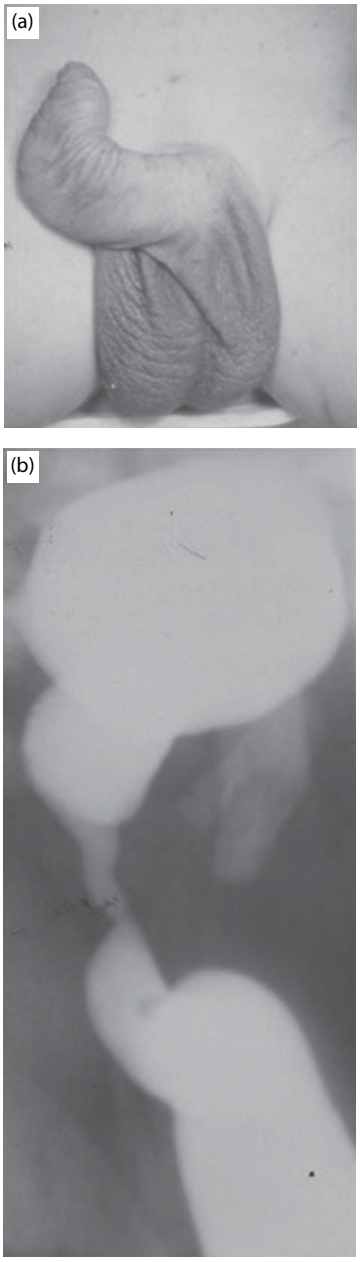

FIGURE 65.13 (a) A newborn with prune belly syndrome and megalourethra. (b) Voiding cystourethrogram in this patient demonstrates a large dilated bladder, open bladder neck, dilated posterior urethra, and wide, patent megalourethra. (Courtesy of George W Kaplan, MD.)

The gubernaculum is normally attached proximally to the tail of the epididymis, travels via the inguinal canal, and attaches distally at the pubic tubercle.[70] No histologic abnormality has been noted, and the nerve supply of the gubernaculum is intact.[129]

The etiology of testicular maldescent in prune belly syndrome is multifactorial. Mechanical obstruction by the enlarged bladder is contributory, as the incidence of cryptorchidism is increased in other diseases associated with an enlarged bladder, such as posterior urethral valves.[130] The mechanical effects of the intramuscular pressure of the abdominal muscles pushing the testis toward the scrotum,

are obviously deficient in the prune belly syndrome. In addition, given the mesenchymal abnormalities of the syndrome, the ability of the gubernaculum to respond hormonally to guide the testes to the scrotum may be impaired.[87]

Comparative quantitative analysis of spermatogonia in fetuses with prune belly syndrome has demonstrated a significantly decreased number of spermatogonia and marked Leydig cell hyperplasia. These changes are evident before expected testicular descent, implying intrinsically abnormal testes.[131] Absent spermatogenesis due to prolonged intra-abdominal location has been histologically documented.[132] Azoospermia was present in adults when a semen sample was obtained.[133] Early orchiopexy is advocated for these patients to optimize potential spermatogenesis, to enable evaluation for malignancy, and to promote better psychological health.[21,134] With assisted reproductive techniques, specifically intracytoplasmic sperm injection, paternity in prune belly patients is possible.[135]

Sexual Function and Fertility

Woodhouse and Snyder studied sexual function in nine adult patients with prune belly syndrome. All had normal libido, with normal erections and orgasms. Seven had retrograde ejaculation. All patients studied to date are azoospermic on semen analysis.[20,133] These patients all had orchiopexy performed late in childhood. Earlier orchiopexy may improve spermatogenesis because germ cells have been found in these patients.[134]

There is no report of a patient with prune belly syndrome becoming a father naturally. However, the first reported case of paternity in a prune belly patient involved the use of intracytoplasmic sperm injection (ICSI) and produced twins.[135] It was subsequently reported that prune belly syndrome is not transmitted to male offspring using ICSI (Table 65.1).[136] Additionally, the first successful pregnancy of a female patient with prune belly syndrome has been reported (Table 65.1).[137] Male patients with prune belly syndrome have multiple factors, other than spermatogenesis, that contribute to infertility. An open bladder neck and poorly developed prostate result in retrograde ejaculation. Associated abnormalities of the prostatic epithelium and seminal vesicles affect the amount and content of the seminal fluid. Vas deferens obstruction and epididymal abnormalities associated with maldescent affect sperm delivery and maturation.

PATIENT EVALUATION

Prenatal

Prenatal diagnosis of prune belly syndrome has been made as early as 11 weeks of gestation on ultrasound.[138] With improved ultrasonic capability and surveillance protocols, the ability to diagnose major genitourinary abnormalities in the early gestational period has increased.[139] However, distinguishing among causes of hydronephrosis, such as posterior urethral valves, can be difficult. Reported ultrasonic diagnostic accuracy varies from 30% to 85%.[140]

The development of vesicoamniotic shunt procedures make possible in utero treatment of patients with obstructive uropathy.[141–143] Specific criteria for in utero intervention include: normal karyotype, severe oligohydramnios, and predicted good renal function.[142,144] The timing for intervention is critical as renal dysplasia is more pronounced with increasing gestational age. Although several reports of vesicoamniotic shunt procedures for fetal obstructive uropathy exist, reviews have failed to document a beneficial effect of fetal intervention on subsequent renal function.[140,145]

Hence, prenatal intervention to relieve potential obstruction in a fetus is difficult to justify. As the majority of patients with prune belly syndrome have no demonstrable evidence of obstruction and renal function does not correlate with the amount of dilatation present in the urinary tract, the risks and benefits of in utero intervention must be carefully weighed.[77,146,147]

Newborn

The appearance of the abdominal wall is diagnostic in the newborn. Given the wide range of disease severity, a multisystem evaluation to rule out significant cardiac, pulmonary, or other associated malformations must take place in the neonatal period.[94] An immediate chest x-ray is necessary to exclude associated pneumothorax and pneumomediastinum. The presence of severe pulmonary hypoplasia affects prognosis in the progressive inability to oxygenate the infant. Antenatal oligohydramnios in these infants indicate impaired renal function.[28]

Initial creatinine measurements reflect maternal renal function and repetitive sampling is necessary. If after 48–72 hours the serum creatinine is greater than 1.0 in the term infant or 1.5 in the preterm infant, a degree of renal insufficiency is present. A progressive rise in serum creatinine over the first few weeks of life, portends a poor outcome. If initial nadir creatinine is less than 0.7 mg/dl, then subsequent renal failure is unlikely.[148] Urine is sent for baseline culture and antibiotic prophylaxis is initiated. Measurement of serum and urinary electrolytes at birth can be helpful in assessing sodium conservation, implying adequate renal function.[149] In the premature and full-term infant, the glomerular filtration rate is initially low, then rapidly increases.[150] This must be remembered in relation to the administration of intravenous contrast agents, which may rapidly elevate plasma osmolality, causing intraventricular hemorrhage as well as further impairment of renal function.[151]

Diagnostic Evaluation

A thorough urologic evaluation proceeds after stabilization of the patient due to other comorbidities. Physical examination and ultrasonography of the urinary tract are initially required. Renal sonograms provide information on cortical thickness, presence of cystic changes and renal size. Sonographic examinations before and after voiding give a clue to the presence of vesicoureteral reflux and post void residual urine. Serial serum electrolyte determinations, urinalysis and urine culture are essential.

Radiologic assessment in the newborn is tempered by the known risks of intravenous contrast and the introduction of infection with retrograde studies. Initially, a

voiding cystourethrogram (VCUG) is performed in those infants with abnormal renal function to insure that a true anatomic, urethral obstruction is not present. This "lethal variant" and the potential confusion with posterior urethral valves "masquerading" as prune belly syndrome must be diagnosed, as treatment changes dramatically.[30,152,153] In addition, the VCUG demonstrates vesicoureteral reflux in up to 85% of patients and assesses bladder emptying. All infants are treated with antibiotics prior to sterile catheterization to decrease the risk of infection. In general, the radiologic assessment of the urinary tract is tailored by the management philosophy of the individual urologic surgeon. Contrast studies requiring risky instrumentation are avoided in those infants with good renal function.

After initial evaluation, a mercaptoacetyltriglycine (MAG 3) renal scan can provide both functional and anatomic information. Blood flow, differential renal function and drainage in response to furosemide (Lasix) can be assessed and compared with subsequent studies. The limitations of diuresis renography in demonstrating obstruction in patients with prune belly syndrome have been noted. A Whitaker test is occasionally necessary as the definitive study to demonstrate significant obstruction, although this is mostly of historical significance.[109] Dimercapto-succinic (DMSA) acid renal scan is performed rather than an excretory urogram (IVP) to evaluate renal size, tubular mass, and differential function. Comparative studies are invaluable to assess renal growth and scarring as these patients require long-term follow up.[154] Some groups have advocated for magnetic resonance urography (MRU) in these patients due to its high resolution and excellent functional and anatomic data.[155] However, the clinical significance of long-term follow-up with MRU remains to be determined.

PATIENT MANAGEMENT

The overall goals of initial management are to preserve renal function and prevent infection. The attainment of these goals are possible via a variety of therapeutic approaches, which range from watchful waiting to immediate surgical reconstruction of the urinary tract.[13,17,19]

Early surgical intervention in the neonate is avoided, unless a rising creatinine or infection occurs, requiring early vesicostomy. Unless salvaged by extraordinary means (extracorporeal membrane oxygenation with or without dialysis), patients with *Category I* disease associated with prenatal oligohydramnios and postnatal pulmonary hypoplasia usually die in the immediate postnatal period due to pulmonary complications. In those few infants surviving the pulmonary insult, high urinary diversion by cutaneous pyelostomy has been attempted to provide optimal urinary drainage.[31] Unfortunately, recovery of renal function is not usually possible as a result of severe underlying renal dysplasia.

Patients with *Category II* involvement are serially monitored for infection and a decrease in renal function. These infants and children are placed on long-term prophylactic antibiotics. With documentation of infection, failure of adequate renal growth, or decreasing renal function, aggressive reconstruction of the urinary tract is pursued. To allow pulmonary maturation, surgical reconstruction is usually delayed until the infant is 3 months of age or more. Our approach involves a surgical remodeling to eliminate urinary stasis and vesicoureteral reflux, and promote optimal urinary drainage (Figures 65.14 and 65.15).[17] If renal insufficiency is severe or infection is initially present, a period of urinary diversion by means of cutaneous vesicostomy is recommended.[156] Cutaneous ureterostomies probably add little to improve drainage. In addition, the upper ureter is anatomically and histologically the most normal and should be preserved if later tailored reconstruction is elected.[84,112] Combining urinary tract reconstruction, orchiopexy, and abdominoplasty at or prior to one year of age is our preferred approach. This optimizes the potential for improved urinary drainage, as well as addressing the issues of subsequent fertility and psychological well-being.[21]

Patients with *Category III* prune belly syndrome demonstrate good renal function, despite gross dilatation of the upper and lower urinary tract and constitute the majority of patients. Serial assessment of renal function by selective imaging techniques is performed. Surgical intervention to reconstruct the urinary tract is not usually necessary. Antibiotic prophylaxis is recommended. Development of urinary infections or decrease in renal function mandates urodynamic assessment of the urinary tract. The demonstration of significant residual urine with unbalanced voiding, warrants surgical intervention to promote emptying.[26,117] Upper tract stasis should be evaluated and a Lasix renal scan performed, to rule out obstruction.[157] The results of these specific tests will help determine the type of surgical intervention. These patients benefit from early orchiopexy and abdominoplasty as correction of the abdominal wall may improve defecation and voiding efficiency.[158]

OPERATIVE INTERVENTIONS IN PRUNE BELLY SYNDROME

In Utero Intervention

With improved maternal–fetal advanced imaging and diagnostic techniques, prune belly syndrome can be suspected by imaging early in pregnancy. Intervention in these patients usually addresses the cause of amniotic fluid reduction which leads to oligohydramnios or anhydramnios. The reduced or absent volume of amniotic fluid is associated with pulmonary hypoplasia, the leading cause of perinatal mortality. Vesicoamniotic shunting can be a consideration with a normal fetal karyotype, limited extent of other detected congenital anomalies, and serial favorable fetal aspirated urinalyses. Vesicoamniotic shunting in patients with suspected bladder outlet obstruction does not improve renal outcomes, but would assist in pulmonary maturation and function.

Anesthetic Considerations

The patient with prune belly syndrome presents unique problems to the anesthesiologist. Several reports have commented on respiratory difficulties due to the abnormal mechanics of pulmonary ventilation. The deficient

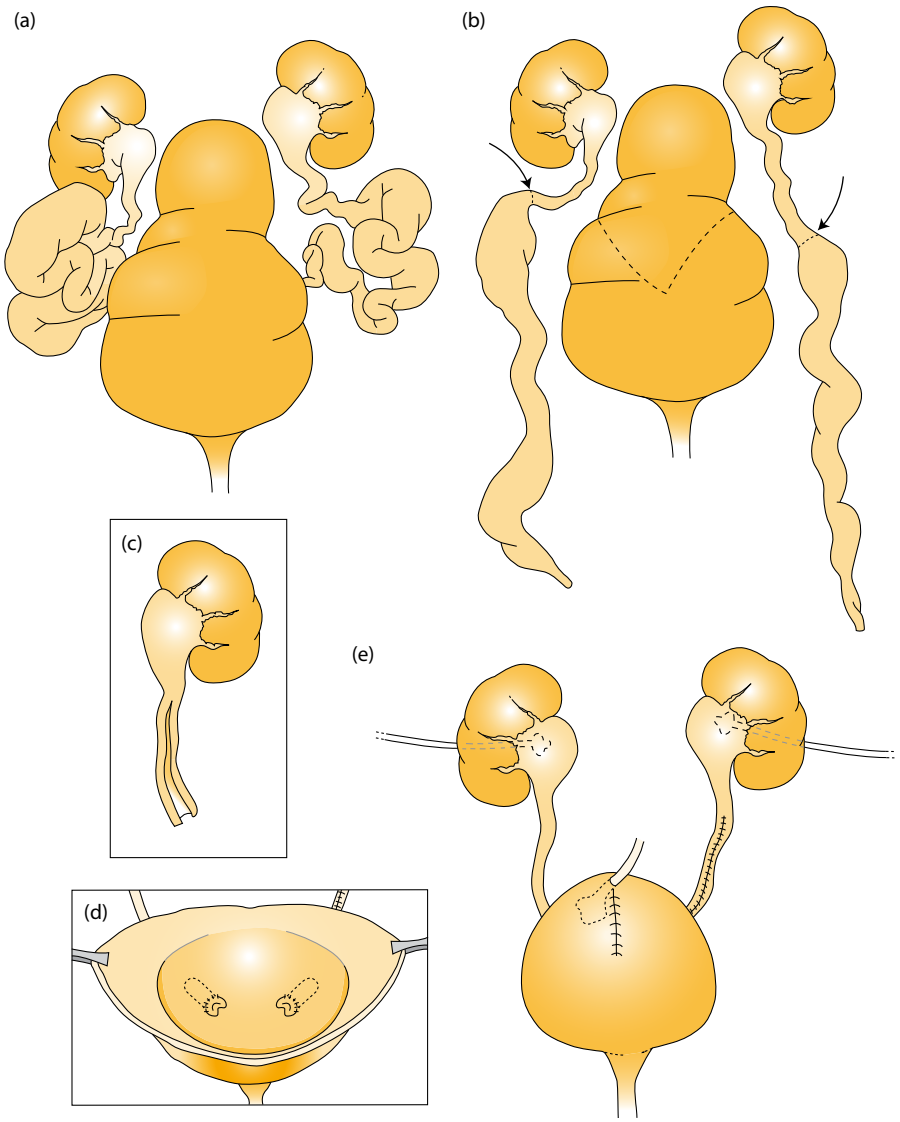

FIGURE 65.14 (a–e) Surgical technique used for extensive reconstruction of prune belly uropathy. The operation is performed transperitoneally. No attempt is made to straighten the lower ureter, as only the upper portion of the ureter is needed for reimplantation. The ureter may require tapering. The dome of the bladder is excised (b. dotted line) in most patients. Ureteral stents (not shown) are used; nephrostomy tubes are rarely required.

abdominal musculature weakens the ability to cough effectively and predisposes these patients to postoperative atelectasis and infection.[159] In one case, prolonged, postoperative ventilation was necessary to effectively clear secretions and adequately oxygenate the patient.[160] In a review of 36 patients with prune belly syndrome, postoperative respiratory infection developed following eight of 133 anesthetics, all of which resolved with antibiotics and physiotherapy.[161] There were no intraoperative respiratory difficulties. Three deaths occurred in the postoperative period; one of which was partially contributed to by pneumonia, as a result of ineffective cough.

All patients with prune belly syndrome require careful preoperative pulmonary assessment. An antecedent history of recurrent respiratory infections warrants aggressive physiotherapy, postural drainage, and intermittent positive pressure breathing treatments. Specific antibiotic therapy should be given.[160] Judicious use of postoperative analgesics, which may produce respiratory depression, is advised.

Vesicourethral Dysfunction

Internal Urethrotomy

In rare cases, an internal urethrotomy is indicated in patients with an anatomic urethral obstruction. At the junction of the prostatic and membranous urethra, a "Type 4" valve may be present. This redundancy partially obstructs the membranous urethra. A transurethral incision at the 12 o'clock position has been advised to improve voiding and decrease residual urine.[162]

Urodynamic assessment, including pressure flow studies, in patients with prune belly syndrome may prove valuable.[5,10,117] The demonstration of residual urine with

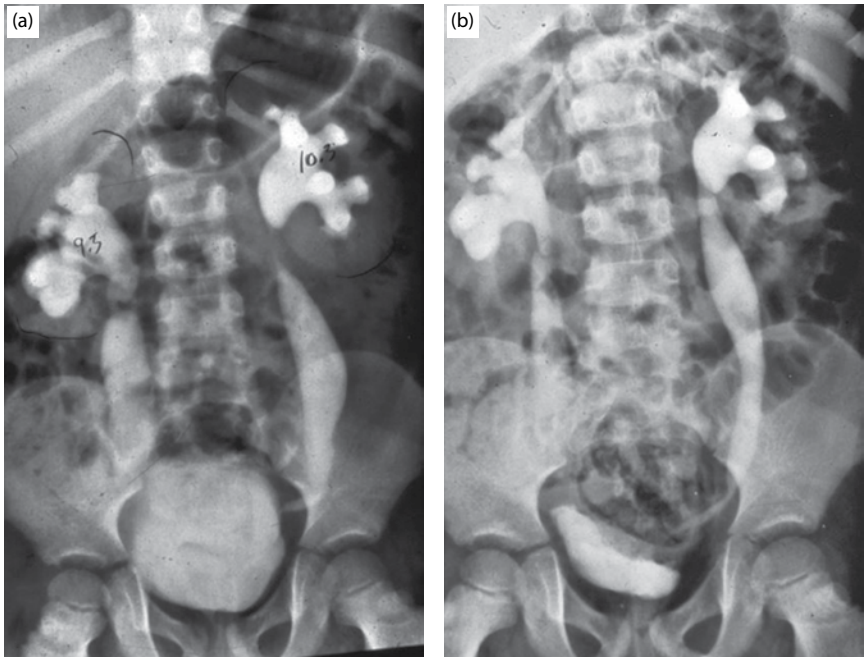

FIGURE 65.15 (a) and (b) Intravenous pyelogram (two views) obtained postoperatively in a child with prune belly syndrome after a single, comprehensive reconstruction.

infection indicates the need for further testing. If a low flow rate is associated with significant residual urine and normal voiding pressure, then intervention to lower urethral resistance is warranted.[117] Endoscopic urethrotomy by hot or cold knife, to decrease outlet resistance, was successful in 10 of 11 cases improving emptying.[163] Most authors who advocate minimal surgical intervention stress the need to closely monitor patients in follow up. Assessment of lower urinary tract dynamics, routine urinary flow rates, and the amount of residual urine are monitored with follow up. Internal urethrotomy is a potential first step to balanced voiding, but clean intermittent catheterization should be considered if the urodynamic criteria of outlet obstruction are not present.[19,116,117,163]

Vesicostomy

When the patient's condition is complicated by urinary infection or deteriorating renal function in the perinatal period, a cutaneous vesicostomy is the drainage procedure of choice.[3,164] This provides a vent that decompresses the entire urinary tract. The vesicostomy is performed through a small transverse incision midway between the umbilicus and the pubic symphysis. The rectus fascia is incised and a small amount of it and the skin removed. The dome of the bladder is mobilized and brought to the skin. The wall of the bladder is sewn to the fascia and matured to the skin. A generous stoma is advocated to prevent stomal stenosis.[109] A urachal diverticulum can be excised, if present. The vesicostomy can serve as an initial temporary drainage procedure prior to more extensive reconstruction.[165] A potential disadvantage is ineffective drainage of the redundant, tortuous, upper ureters or an associated ureteropelvic junction obstruction. This is unlikely, as true supravesical obstruction is rarely a component of prune belly syndrome.

Reduction Cystoplasty

Reduction cystoplasty has been suggested in order to reduce volume and improve emptying.[113] Bladder volumes in excess of 3 L have been recorded in children with prune belly syndrome.[117] Concomitant removal of a dilated urachal diverticulum, which contributes to inefficient voiding, is performed. According to the law of LaPlace, a spherical shape of the bladder should allow maximal intravesical pressure with each detrusor contraction. A variety of techniques to reduce bladder volume and produce a more efficient spherical shape have been proposed.[23,113,166] A vest–over-pants closure of the bladder wall after removal of bladder epithelial strips or simple resection and watertight closure has been performed in the majority of cases.

Reduction cystoplasty has clinically resulted in fewer hospitalizations for urinary infections and initially improved voiding. However, the long-term bladder capacity and voiding efficiency were not improved.[167] Comparison of urodynamic voiding parameters between reconstructed voiding patients and non-reconstructed voiding patients did not show significant differences. Consequently, some authors do not recommend reduction cystoplasty in light of the effective and safe application of clean intermittent catheterization except for the removal of a urachal pseudodiverticulum.[109,116]

Anterior Urethra

Prune belly syndrome is associated with microurethra and megalourethra. Utilization of the unused "micro" anterior urethra is advocated. Successful progressive soft dilation or intermittent hydrodistension of the urethra with normal voiding has been reported.[123,168] If the anterior urethra is not usable, urethroplasty techniques combining skin flaps

and grafts are necessary to bridge the anterior urethral defect. Megalourethra can be repaired by application of hypospadias operative techniques.

Upper Urinary Tract

Vesicoureteral Dysfunction

Vesicoureteral dysfunction is manifested most commonly as vesicoureteral reflux in up to 85% of patients. Ureteral valves and ureterovesical junction obstruction have been described.[110] Both conditions potentially contribute to urinary stasis, and increased risk of infection. The indications for surgical correction of obstructing lesions should be based on the demonstration of decreasing renal function, infection, or parental preference at the time of comprehensive reconstruction.

Surgery to repair vesicoureteral reflux has been contested because of the poor peristaltic activity of the ureters and their dissipation of voiding pressure due to increased capacity.[3] Observation of these patients, who remain infection free on or off prophylactic antibiotics, has confirmed preservation of renal function.[12,26] When urinary infection becomes problematic, correction of reflux and reduction of urinary stasis become necessary. Formal tapering and reimplantation, as well as ureteral imbrication have been used as part of the comprehensive approach to management.[21] We found no difference in the complication rate with either procedure, and 9 of 13 patients had successful elimination of their reflux. Ureteral imbrication may produce fewer problems with stenosis.[3] However, the imbricated ureter is very bulky requiring a long, wide subepithelial tunnel for reimplantation.

Temporary diversion of the upper tract by pyelostomy or ureterostomy is rarely necessary. Vesicostomy is preferred, but in those neonates with unresponsive urosepsis, high diversion to optimize drainage may be required.

Cryptorchidism

The early correction of the cryptorchid intra-abdominal testes by a transabdominal approach is recommended to optimize spermatogenesis, facilitate examination for testicular malignancy, and improve testicular salvage. If orchiopexy is performed in the first year of life, a standard technique with preservation of the spermatic vessels can usually be performed pending testis location. Orchiopexy in older children frequently requires division of the spermatic vessels, with results based on a one- or two-stage Fowler-Stevens technique.[169–171] To avoid atrophy, a broad, peritoneal pedicle mobilized with the long-looping vas; combined with early ligation of the spermatic vessels above the point of confluence of the vas and spermatic artery is recommended.[172] Utilizing this two-stage approach, an 80%–83% success rate for intra-abdominal testes has been attained.[170,171] Overall, successful orchiopexy can be expected in the majority of patients.

Open and laparoscopic techniques have been described with similar results.[173–175] Unique technical considerations exist with the laparoscopic approach in these patients. A lax abdominal wall creates technical challenges that are not present in other infants/children. With the thin abdominal wall, air leak can be troublesome, hence, lower abdominal pressures are need for insufflation with smaller port site incisions. In addition, longer working instruments may be required.[176,177] Open or laparoscopic orchiopexy can be performed at the time of comprehensive reconstruction with a high success rate.[17–19,178]

Microvascular testicular autotransplantation has been utilized in patients with prune belly syndrome. The spermatic vessels are anastomosed to the inferior epigastric vessels, with microsurgical vascular techniques.[179] This has normally been performed in older patients as a last salvage effort.[165] Prior to 1999, all boys with prune belly syndrome were considered infertile. However, with recent advances in male factor infertility and assisted reproductive techniques, the first assisted conception of a man with prune belly syndrome was reported.[135] Consequently, an early orchiopexy to preserve spermatogonia and testicular function in these patients is warranted.

Abdominal Wall Reconstruction

Abdominal wall reconstruction has a significant role in the treatment of patients with prune belly syndrome. Abdominoplasty had previously been performed to improve body image, self-esteem, and psychological well-being.[22–24] Recent studies suggest that the improved abdominal contour, with repositioning of the most functional musculature, improved voiding efficiency.[106,158] The decrease in residual urine has obvious benefit in the prevention of urinary infection. In addition, abdominoplasty was subjectively felt to improve defecation and sensation of bladder fullness.

The surgical approaches to performance of the abdominoplasty are based on preservation of the lateral and upper parts of the abdominal wall, the sites of most normal musculature. Our early experience was quite positive with the cosmetic and functional results provided by the abdominoplasty as described by Randolph et al.[107] This technique excises the most abnormal segment of redundant abdominal wall, provides excellent exposure for urinary reconstruction and orchiopexy, and preserves segmental motor nerves to the retained abdominal musculature. In 16 patients where this technique was utilized, 9 had an excellent cosmetic improvement in abdominal contour and in 7 a slight protuberance remained. There were no serious complications related to the abdominoplasty procedure (Figures 65.16 and 65.17).[21] The major criticisms of this technique are that it does not improve abdominal wall thickness, and lateral bulging is not completely eliminated. However, this technique has been favored by a number of surgeons historically.[3,109]

More recently, a surgical approach to abdominal wall reconstruction, utilizing a ellipsoid midline incision with extensive subcutaneous dissection, and a pants over vest closure has been described (Figures 65.17 and 65.18).[23,180–182] This technique preserves the umbilicus, uses the full thickness of abdominal wall, and provides narrowing at the waist. Excellent cosmetic results with a high degree of patient satisfaction have been reported with both the Ehrlich and Monfort techniques (Figures 65.19 and 65.20).[180,181] An adaptation utilizing an extraperitoneal

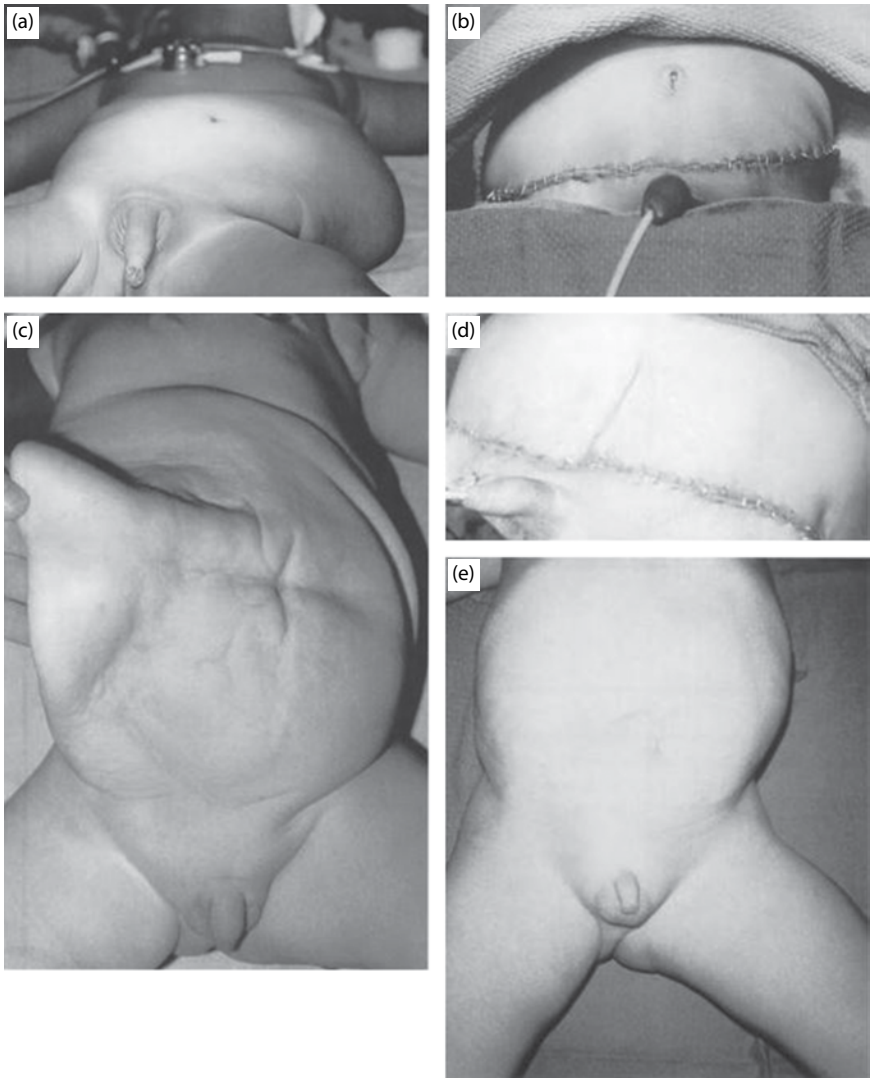

FIGURE 65.16 (a) Preoperative depiction of a 2-year-old child with bilateral cutaneous loop ureterostomies prior to comprehensive surgical reconstruction. (b) Same child after comprehensive reconstruction of the urinary tract and Monfort abdominoplasty. (Courtesy of George W Kaplan, MD.)

plication of the abdominal wall through a midline incision decreases the extent of facial dissection, avoids entering the peritoneal cavity, and decreases postoperative recovery time.[183] This simplification seems most appropriate for patients not requiring other concomitant surgical procedures. A modification of the Monfort abdominoplasty includes a neoumbilical revision to provide a normal anatomic placement of the umbilicus (Figure 65.21).[184]

Other modifications to this approach have continued to evolve over the last couple decades. For instance, varying the width of the central plate can be used to correct asymmetry.[185,186] Additionally, central plate plication has been reported to reduce vertical redundancy, and flank plication to decrease fascial weakness.[186] The use of laparoscopy for visualization of intra-abdominal contents and assistance in abdominal wall reconstruction has also been described by several centers.[186,187] Functional and aesthetic outcomes have been excellent with these advancements, although "retightening" of the fascia has remained a persistent challenge (Table 65.4). Fearon et al. report successful reduction of this complication with the use of rectus femoris muscle transpositions (Table 65.4[188]).

Other treatment possibilities include abdominal binders and elasticized corsets. These aids do not address the psychological implications of the abdominal disfigurement, which have generally been ignored in the past.[180] The importance of body image during the formative years of childhood cannot be overestimated. The abdominoplasty provides these males with freedom from abdominal binders, a more natural waisted physique, ability to wear normal pants, and participate in sports.[21]

Comprehensive Reconstruction

Comprehensive reconstruction in the prune belly patient involves reduction cystoplasty, resection of the distal ureter and bilateral ureteral tapered reimplantation (see Figure 65.14). Reconstruction may be combined with the performance of the abdominoplasty and bilateral orchiopexy, usually prior to two years of age.[17,22] This aggressive

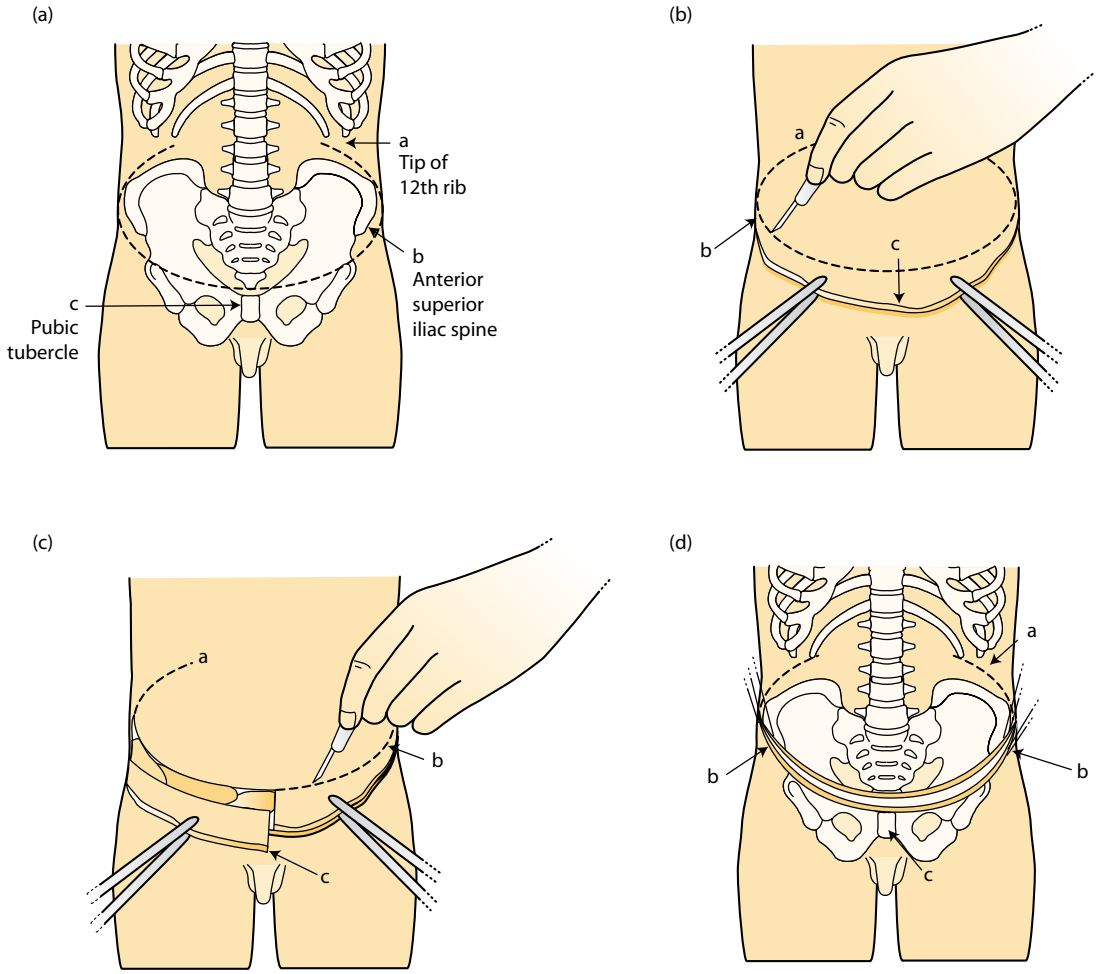

FIGURE 65.17 Technique of the Randolph abdominoplasty. (a) A curvilinear incision extends from the tip of the 12th rib, along the anterior superior iliac spine to the pubic tubercle and onto the opposite 12th rib. (b) A parallel incision is made, avoiding the removal of too much abdominal wall. (c) Rhomboid-like pieces of abdominal wall are removed. (d) Critical non-absorbable sutures are placed at the anterior iliac spines and pubic tubercle. These are placed through full thickness of the abdominal wall including the periosteum.

approach was utilized in 15 patients in our series. Serial measurements of creatinine up to 13 years later documented preservation of renal function.[21] Vesicoureteral reflux was corrected in 9 of 13 patients and improved in 3. Because of the known urinary stasis that occurs in these children, all are maintained on antibiotic prophylaxis. Therefore, our ability to decrease urinary infection cannot be totally attributed to the surgical result.

Complete surgical reconstruction, as reported by Denes et al., involved abdominoplasty, urinary tract reconstruction, and orchiopexy in a select group of 32 patients. A morbidity rate of 18.7% and a re-operation rate of 15.6% was reported. In all, 30 of 32 patients demonstrated stable or improved renal function at a mean follow up of 5 years.[178]

One surgical approach is that proposed by Woodward (see Figure 65.14). A wide lower abdominal incision is made that extends from the tip of the 12th rib, along the anterior superior iliac spine to the pubis and then curves upward to the opposite 12th rib.[107] This tends to spare the segmental nerve and vascular supply of the abdominal wall left for reconstruction. In addition, at the time of excision of the redundant abdominal wall, that portion with the most muscle fibers is preserved. The exposure of the urinary tract provided with this incision is exceptional. However, use of this technique has decreased given concerns regarding interruption of the epigastric vessels and redundant lateral abdominal tissue. Instead, most surgeons favor the Monfort approach as described above (see Figure 65.21).

The posterior peritoneum is incised along the length of the ureters. The spermatic vessels are mobilized distally; care being taken not to compromise the peritoneal attachments of the vas deferens if a Fowler-Stephens orchiopexy is required. The bladder is opened in the midline with cautery. The laterally placed ureteral orifices are recognized and each ureter is mobilized. The extreme length of the mobilized ureters allows for resection of its distal third, usually the most abnormal portion. Formal tapering or imbrication is performed (Figure 65.22).[189,190] The ureters are then reimplanted, using a transtrigonal or Leadbetter Politano technique. Stenting of the operated ureters is performed and these are brought out through the bladder and separate abdominal incisions.

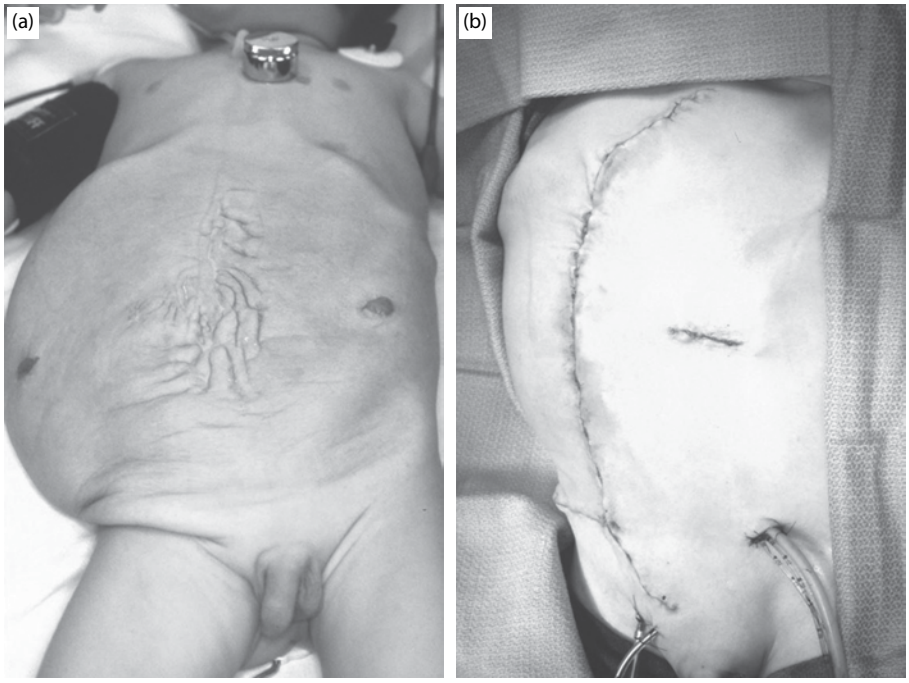

FIGURE 65.18 (a, b) Preoperative and immediate postoperative results of a Randolph abdominoplasty. (c–e) Preoperative, postoperative, and 18 months following Randolph abdominoplasty in a 9-month-old child.

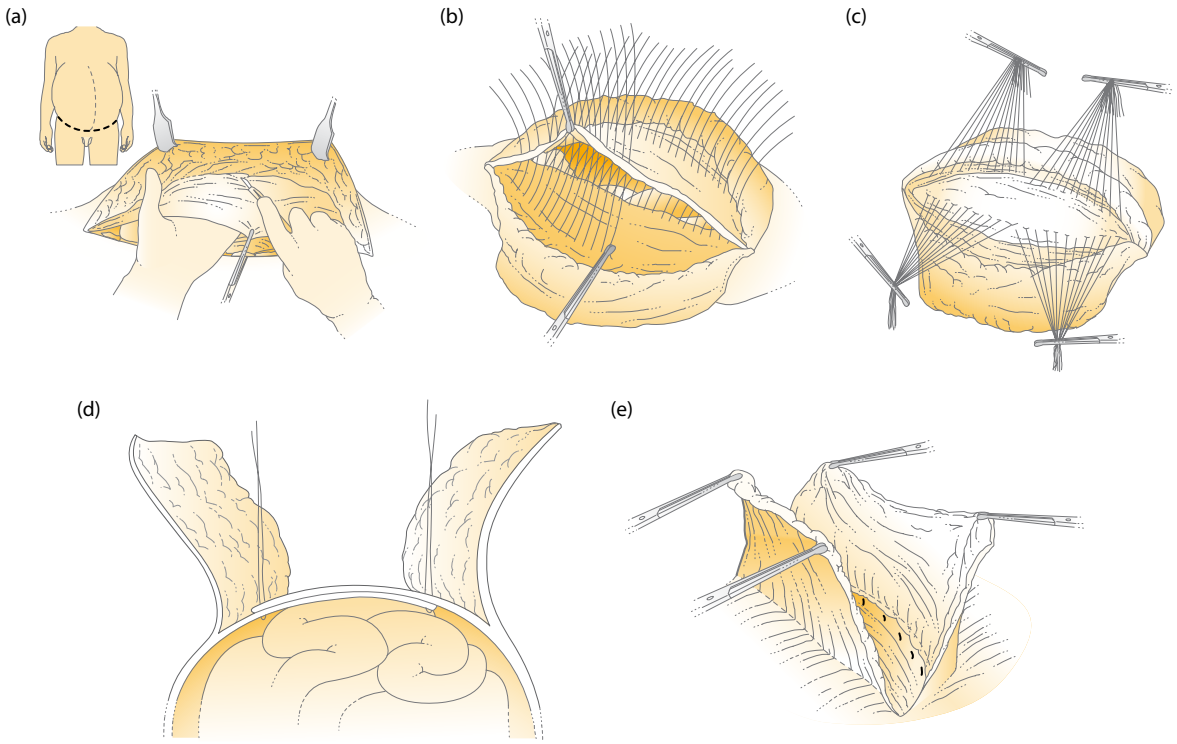

FIGURE 65.19 Ehrlich abdominoplasty. (a) Sharp dissection separates the skin the subcutaneous tissue from the musculofascial layer. (b–d) A vest–over-pants closure of the musculofascial layers. The umbilicus can be saved on a separate pedicle. (e) The excess abdominal skin is removed. (Reproduced from Ehrlich RM et al. *J Urol* 1986;136(1):282–5. With permission from Williams & Wilkins.)

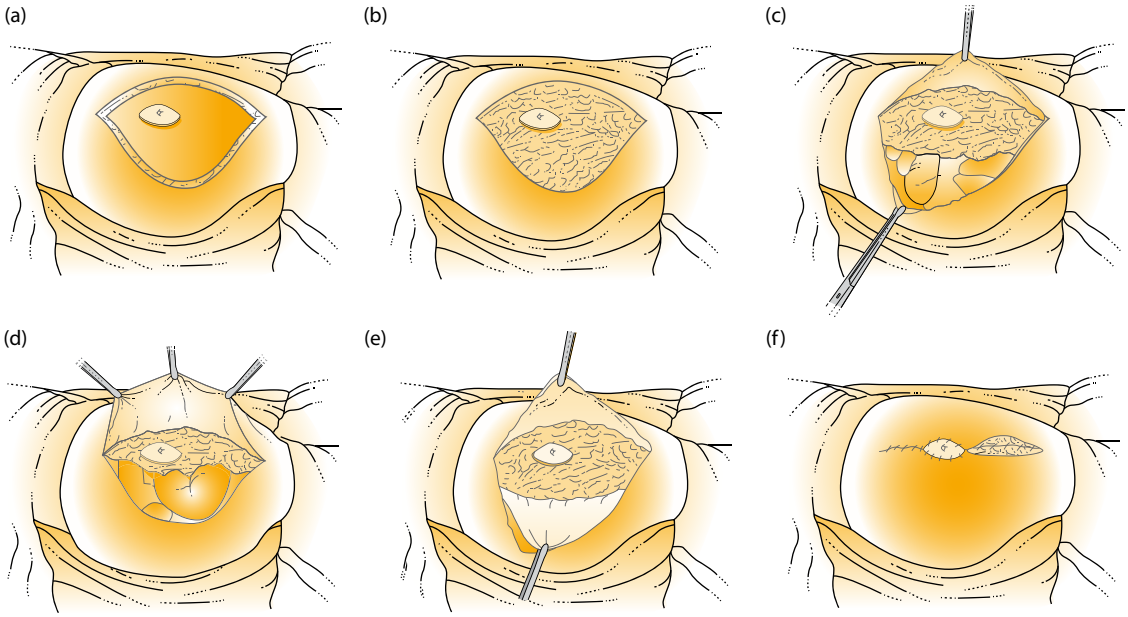

FIGURE 65.20 Monfort abdominoplasty. (a) An almond-shaped incision is made on the abdomen from the xyphoid to the pubic symphysis. (b) The full thickness of skin is removed, sparing the umbilicus. (c) The peritoneum is opened lateral to the musculofascial later. Intra-abdominal surgery can be easily performed through these incisions. (d) The parietal peritoneum is incised at a level to achieve a normal-appearing waistline. (e) The edges of the musculofascial plate are sewn to the peritoneal incisions. (f) The lateral skin flaps are trimmed and sutured together in the midline. (From Monfort G et al. *J Urol* 1991;146(2):639–40. With permission from Williams & Wilkins.)

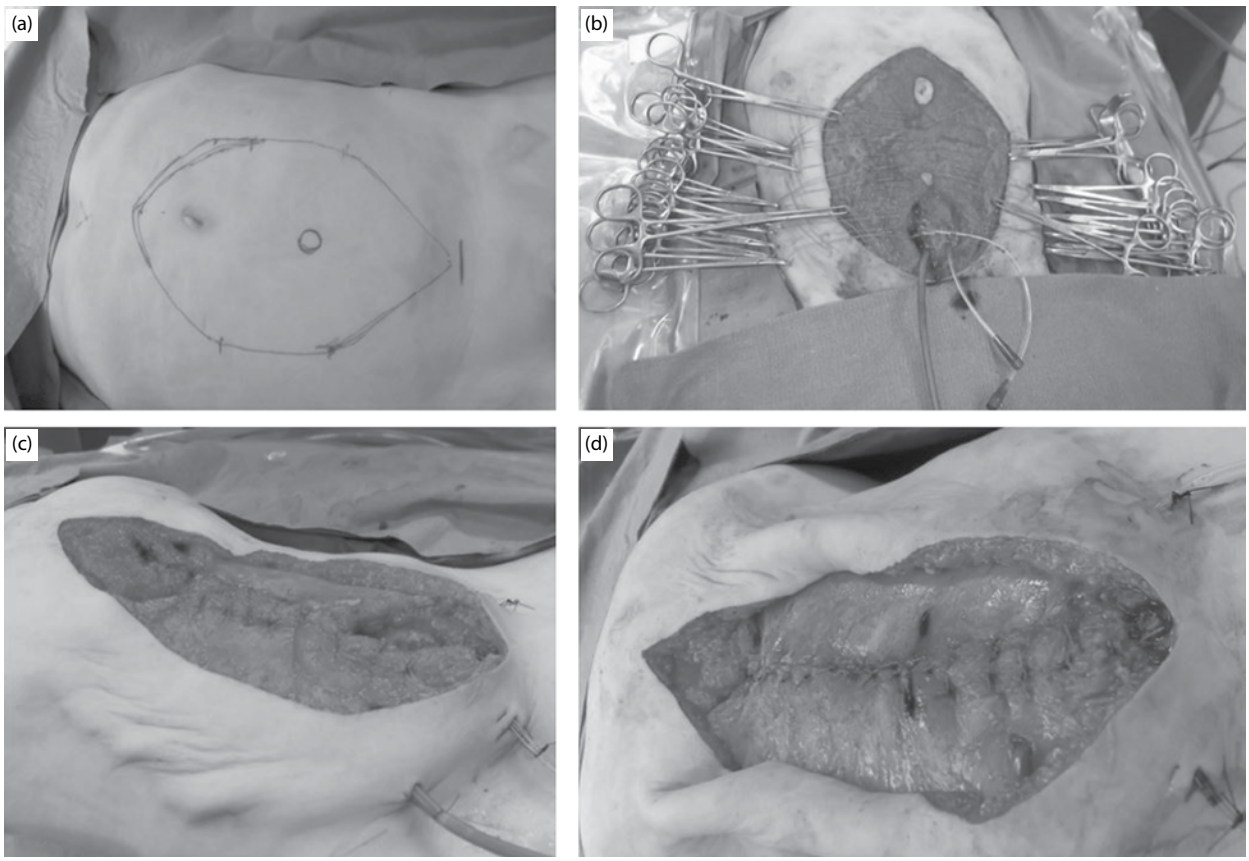

FIGURE 65.21 Modified Monfort abdominoplasty. (a) Incision mapping with neoumbilicus marked. (b) A vest-over-pants closure of the musculofascial layers with ureteral catheters and suprapubic catheter in place. (c) Imbrication of musculofascial layers. (d) Completed closure of musculofascial layers.

TABLE 65.4 Contemporary abdominoplasty techniques and outcomes in prune belly syndrome

	No. of patients	Type of repair	Umbilical ischemia	Complication (other)	Retightening required	Aesthetic result	Functional result	Follow-up (years)
Denes et al.[193] São Paulo, Brazil	32	Vest over pants	3	3 UTI	2	All improved	Most improved	17
Fallat et al.[21] Washington, D.C.	16	Excision	1	2	7	Nine improved	Nine improved	18
Fearon et al.[21] Dallas, TX	13	Vest over pants, RFMT	1	1 UTI, 1 chylous leak	0	All improved	All improved	6
Furness et al.[183] Chicago, Ill.	13	Plication	NR	NR	3	All improved	NR	7
Lesavoy et al.[192] Los Angeles, CA	20	Vest over pants	2	1 infection	3	All improved	Most improved	25
Smith et al.[186] Atlanta, GA	16	Vest over pants, flank plication[a]	0	1 suture erosion	1	All improved	All improved	12

Source: Adapted from review article by Fearon JA, Varkarakis G. *Plast Reconstr Surg* 2012;130(3):648–57 and data from Lopes RI et al. *J Pediatr Urol* 2015;11(5):276.e1–7; Fallat ME et al. *J Urol* 1989;142(3):802–5; Furness PD et al. *J Urol* 1998:1195–7; Lesavoy MA et al. *Plast Reconstr Surg* 2012;129(1):104e–9e; Smith EA et al. *J Pediatr Urol* 2017;13(5):502.e1–e6.

Abbreviations: UTI, urinary tract infection; NR, not reported; RFMT, rectus femoris muscle transposition.

[a] Diagnostic laparoscopy performed.

Prior to reduction cystoplasty, the testes are mobilized with a wide apron of posterior peritoneum (Figure 65.23). In some cases, the testes may be adherent to the enlarged bladder and must be meticulously mobilized to preserve blood supply (Figure 65.24). If the reconstruction is performed prior to 2 years of age, a standard orchiopexy with intact spermatic vessels can be performed 80% of the time.[18,21] Otherwise, a delayed or formal Fowler-Stephens orchiopexy will be necessary.[174]

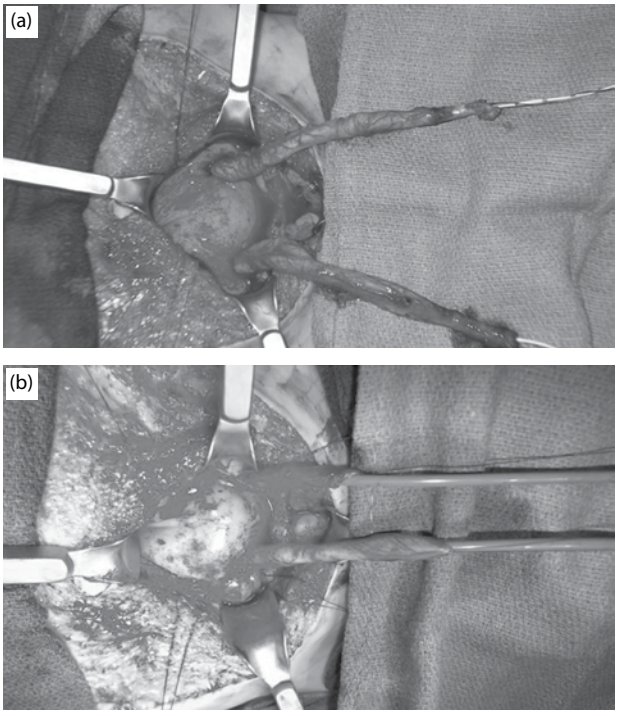

FIGURE 65.22 (a) Both ureters have been mobilized prior to (b) implantation and tapering.

The bladder is reduced in size by resection of the urachal remnant and the huge bladder dome. A strip of bladder epithelium can be removed from one of the lateral walls and closed by the vest-over-pants technique. The bladder is drained with a Malecot catheter. The previously mobilized testes are brought up through the distal abdominal wall at the pubic tubercle. A dartos pouch is created in the scrotum and each testis is secured in the pouch with permanent sutures.

The redundant abdominal wall is then held taut and marked in the midline and laterally at the costovertebral angles to outline the tissue to be excised (see Figure 65.17).[107] Avoidance of removal of excessive amounts of abdominal wall is critical. The second line of incision parallels the previous incision. A large wedge of full thickness abdominal wall is removed. The closure of the abdominal wall is commenced by placement of key sutures of 0 or 1–0 non-absorbable sutures at the anterior iliac spines and at each pubic tubercle. These sutures should include the periosteum of the bone and a full thickness of the proximal opposing tissue edge. The tension created occasionally allows for removal of additional lateral redundant abdominal wall. Each section between the key sutures is closed with interrupted sutures opposing the full thickness of the abdominal tissue. The subcutaneous tissue is closed to prevent dead space and the skin is approximated with a subcuticular absorbable suture. Other techniques include modification of laparoscopic and open approaches with preservation of the umbilicus, "double-breasted" medial fascial closure, and excess abdominal skin removal, in association with urinary tract reconstruction.[187,191–193]

Renal Transplantation

Progressive renal insufficiency resulting from renal dysplasia, reflux nephropathy, and recurrent pyelonephritis can be successfully treated by renal transplantation. Renal transplantation in patients with prune belly syndrome

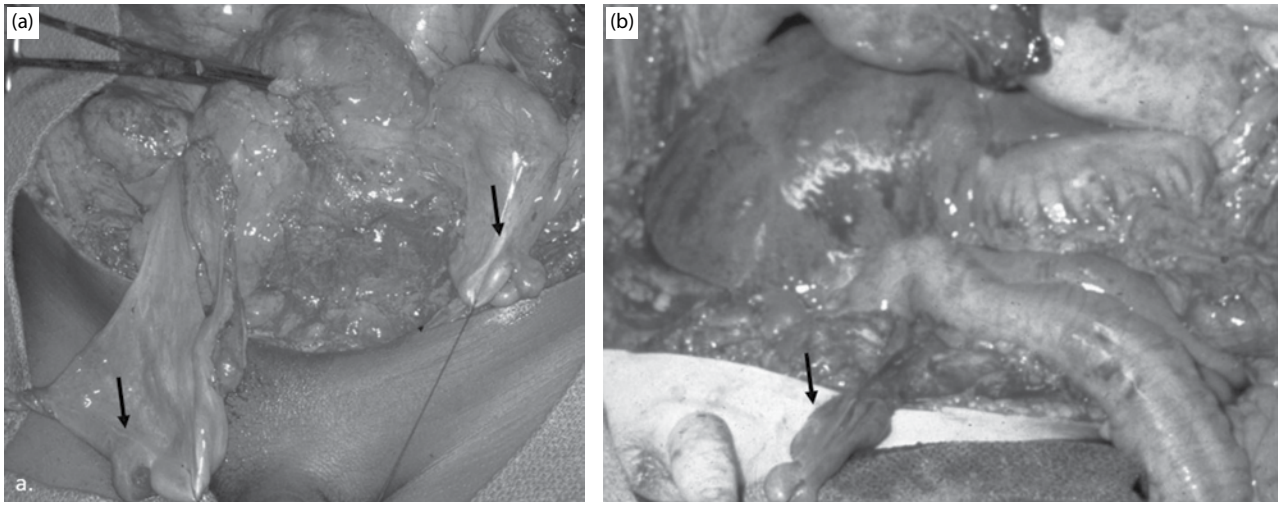

FIGURE 65.23 (a) Widely mobilized peritoneum with intact spermatic vessels (arrows) ensures good blood supply to the testis. (b) Achieving adequate length to secure the testes in the scrotum is usually not difficult in the child less than 2 years of age.

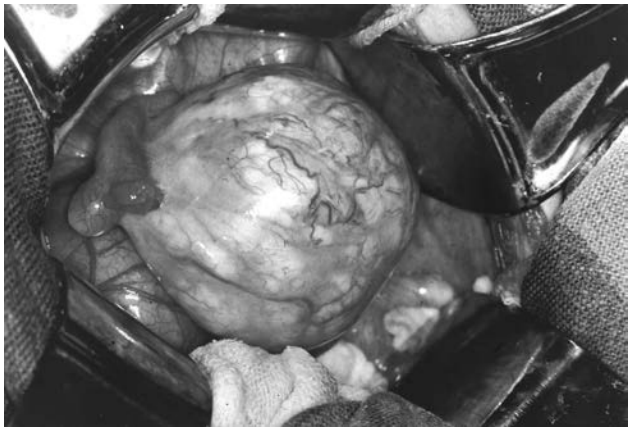

FIGURE 65.24 The intraabdominal testicle is densely adherent to the enlarged bladder. It was meticulously mobilized off its peritoneal attachments and a single-stage Fowler-Stephens orchiopexy was performed to allow normal testicular growth.

was first reported in 1976.[194] The age at transplantation has ranged from 8 months to 21 years of age.[195,196] Both cadaver and living-related donor kidneys have been successfully transplanted. In a retrospective review of eight patients with prune belly syndrome who underwent transplantation, there was no statistically significant difference in patient deaths, graft survival or graft function when compared to age-matched controls.[196] A more recent retrospective analysis of graft survival at 10 years of 47% was not statistically significantly different from age-matched controlled patients.[197] The success of renal transplantation was in part attributed to the low-pressure urine storage provided by the bladder in prune belly syndrome.[198]

Prior to transplantation, bilateral nephroureterectomies were performed in all reported cases. Radiographic and urodynamic assessment of the lower urinary tract is recommended to insure absence of obstruction and balanced voiding.[199] The use of clean intermittent catheterization to empty the decompensated bladder is not a contraindication to renal transplantation.[196,200] All patients should be kept on antibiotic prophylaxis. An unusual complication of transplantation in prune belly syndrome is allograft torsion.[201] The torsion, with resultant graft loss, was a result of lack of abdominal wall tone. Nephropexy has been recommended to avoid this disastrous complication.

Future Considerations

Minimally invasive techniques are more commonly available in the pediatric urologist's armamentarium. Laparoscopic orchiopexy, laparoscopic appendicovesicostomy with robot assistance and laparoscopic-assisted abdominoplasty are increasingly utilized in the management of these patients.[187,191,202,203]

CONCLUSIONS

Given the wide spectrum of disease, the treatment of prune belly syndrome is patient specific. When infection and stasis compromise renal growth or function, aggressive surgical intervention to promote drainage is advised. The testes in these infants are placed in the scrotum early for improved fertility purposes and can be accomplished by laparoscopic or open techniques. Because of the changing urodynamic condition of the lower urinary tract and its effects on renal function and urinary infection, all patients with prune belly syndrome require careful lifelong urologic surveillance.

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CHAPTER 66

Surgical Excision of Urachal Anomalies

Heidi A. Stephany, Jathin Bandari, and Steven G. Docimo

BACKGROUND

The urachus is the fibrous remnant that represents the intraembryonic communication between the bladder and the allantois. The urachus closes by progressive accumulation of desquamated epithelium within the lumen early in gestation and becomes the median umbilical ligament. When this process has been disrupted, a patent urachus or urachal remnant will persist in the form of a cyst, sinus, or diverticulum (Figure 66.1).[1] A complete review of urachal anomalies can be found in Chapter 63.

Indications for excision of urachal anomalies include the risk of malignant change and recurrent infections. Various approaches have been described, including both open and laparoscopic techniques. Regardless of the technique used, surgical excision of a bladder cuff is recommended to ensure that all remnants of the urachus are removed. Cystoscopy to visualize and confirm the anomaly may be of benefit, and placement of a catheter with intermittent distension of the bladder may assist with dissection.

OPEN APPROACHES

Traditionally, the open approach utilizes a low transverse or midline incision. This exposes the bladder so that the urachus may be traced from the bladder dome toward the umbilicus.[2]

Another technique, which is used preferentially by the authors, is using an open, scarless incision. The urachus is circumferentially dissected out down to the bladder dome through a single intraumbilical incision. The umbilicus can then be reconstructed, leaving the patient with no scar (Figures 66.2 and 66.3). This technique is particularly suited to children due to the higher position of the bladder dome, but it has also been used in young adults. Patients are routinely treated as outpatients without bladder catheterization or drains.[3] (Video 66.1).

LAPAROSCOPIC APPROACHES

Alternatively, laparoscopic excision, with or without the use of the da Vinci surgical robot system (Intuitive Surgical, Sunnyvale, California), has also been successful. Advantages of this minimally invasive technique include a panoramic view of the surgical field and improved cosmesis as a result of smaller incisions. There are multiple reports in the literature describing outcomes in small cohorts of patients for this uncommon condition. During dissection, however, care must be taken to not spill infected cyst contents. Cysts are delivered through a trocar site after drainage by needle aspiration.[4] The mean operative times with this approach have ranged from 50 to 180 minutes for traditional laparoscopic techniques.[4–7]

Robotic-assisted laparoscopy has been used increasingly in the pediatric population for a multitude of reconstructive procedures, including excision of urachal remnants.[8] The advantages of robotic-assisted laparoscopy include a high-resolution, magnified three-dimensional view and increased dexterity and articulation of the robotic instruments, all of which can lead to more precision, particularly of benefit with suturing.[9] The first robotic-assisted excision of a pediatric urachal cyst was reported by Yamzon et al. The authors describe using a 30° angled lens positioned upward to allow visualization of the bladder and anterior abdominal wall. Placing the camera port superior to the umbilicus in the midline allows complete resection of the umbilical attachments

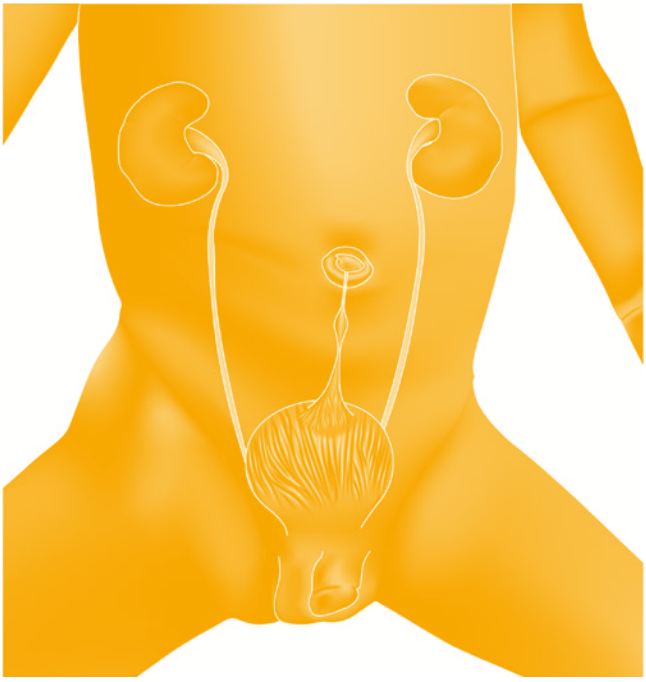

FIGURE 66.1 Urachal remnant.

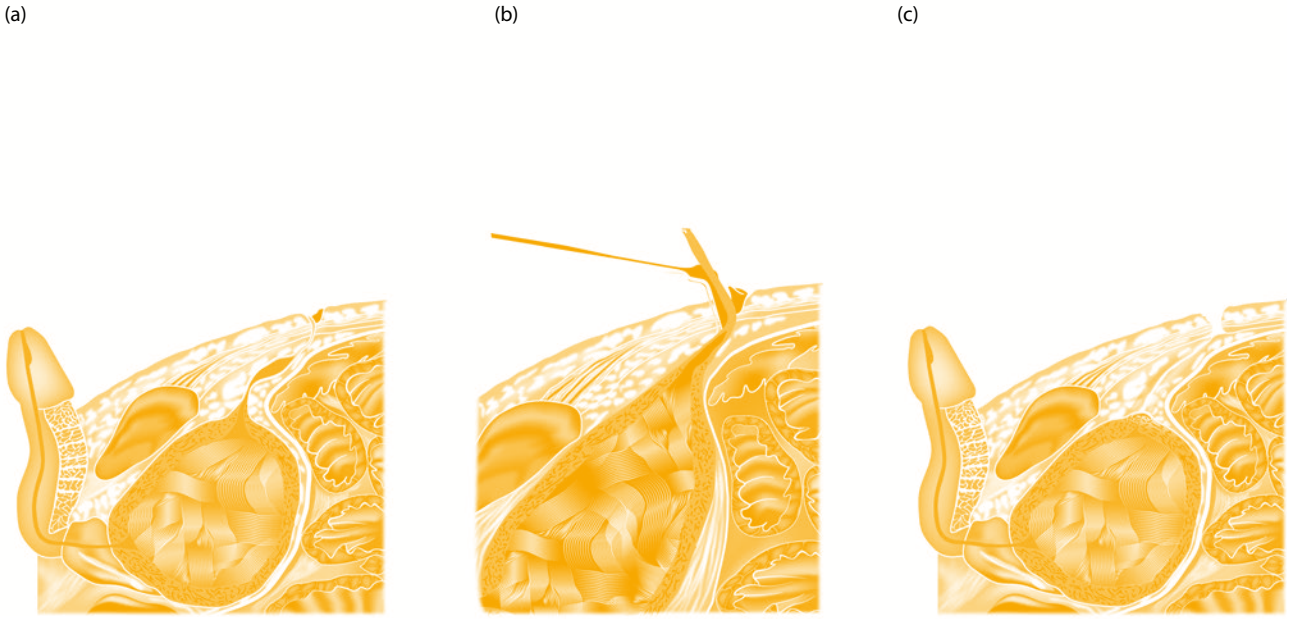

FIGURE 66.2 (a) The umbilicus is everted and stay sutures placed around the edges of the sinus or cyst to assist in retraction. (b) A U-shaped flap is raised at the lower lip of the umbilicus, and a circumferential dissection around the urachus is completed down to the posterior rectus fascia. (c) Stay sutures are placed in the bladder, and a small cuff of bladder is excised with urachus and the bladder closed in two layers.

of the urachal remnant.[10] Robotic assistant arms can be placed above the level of the umbilicus at the anterior axillary line, as described by Yamzon et al., or inferior to the Pfannenstiel line and medial to the anterior superior iliac spine, as recently reported by Rivera et al.[10,11] The urachal remnant is detached superiorly with cautery and taken down from the anterior abdominal wall toward the bladder (Figure 66.4). A hitch stitch can be used to assist with countertraction, as well as stability during sewing. The bladder cuff and remnant are excised, and a two-layer, watertight closure is performed (Figure 66.5).

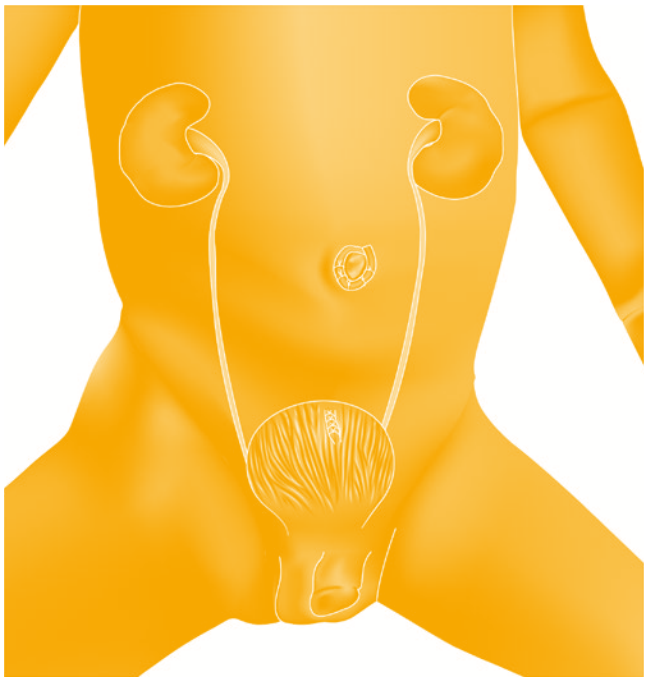

FIGURE 66.3 The rectus fascia was closed, and the umbilicus was reconstructed to its anatomic position.

CONCLUSIONS

Surgical excision remains the mainstay of management for urachal anomalies. The majority of these anomalies can be removed through the base of the umbilicus with no resulting visible scar. Laparoscopic approaches, with or without robotic assistance, have been described with excellent results and recovery. Larger incisions for open removal should only be necessary if there is concern for malignancy, there is active infection requiring drainage and removal,

FIGURE 66.4 Dissecting the urachal remnant from the abdominal wall toward the bladder in a robotic procedure. (Courtesy of Glenn M, Cannon, MD.)

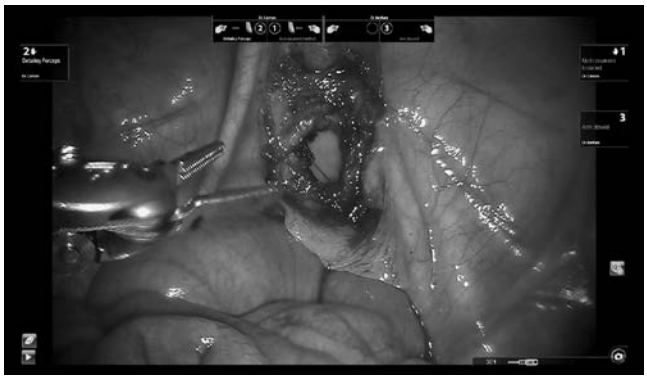

FIGURE 66.5 Cystotomy after remnant and bladder cuff excised robotically. (Courtesy of Glenn M, Cannon, MD.)

or the remnant is too large to be conveniently removed through a minimally invasive approach. Full excision requires removal of a bladder cuff and a watertight closure.

MULTIMEDIA FILES AVAILABLE ONLINE (www.crcpress.com/cw/Docimo)

VIDEO 66.1 Excision of urachal remnant in 15 month child using the open scarless surgical technique.

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Section 6

Urethra, External Genitalia, and Retroperitoneum

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CHAPTER 67

Basic Science of the Genitalia

Laurence S. Baskin

INTRODUCTION

Genital anomalies are the most common birth defects, with the exception of cardiac malformations.

Hypospadias is defined as an arrest in normal development of the urethra, foreskin, and ventral aspect of the penis; it is the most common genital anomaly, occurring in approximately 1:250 newborns, or roughly 1 out of 125 live male births.[1] Hypospadias results in a wide range of abnormalities, with the urethral opening located anywhere along the shaft of the penis, within the scrotum, or even in the perineum (Figure 67.1a–c).[2]

Hypospadias is also associated with ventral penile curvature (chordee). Left uncorrected, patients with severe hypospadias may need to sit down to void and tend to shun intimate relationships because of fears related to abnormal sexuality. Babies born with severe hypospadias and penile curvature may have "ambiguous genitalia" in the newborn period, making an immediate and accurate sex assignment difficult.

Epispadias is a urethral defect on the dorsal aspect of the penis (Figure 67.1d). Epispadias is associated with a short penis, dorsal penile curvature, and in the most severe forms, bladder exstrophy. Females (as well as males) can also suffer from these genital anomalies and others, such as genital duplication or malformations, but these problems are extremely rare (Figure 67.1e and f). Understanding abnormal development of the external genitalia requires a concise knowledge of normal genital development.

NORMAL SEXUAL DIFFERENTIATION

Chromosomal Sex

The genetic material necessary for the development of the male phenotype is normally located on the short arm of the Y chromosome. The critical gene or sex-determining region on the Y chromosome is known as the *SRY* region.[3] The gene products of the *SRY* genetic cascade will subsequently direct the development of the testis by interacting with multiple other genes, such as *SOX-9*. Genetic information that is necessary for male and female development beyond gonadal differentiation is located on the X chromosome and on the autosomes.

Gonadal Differentiation

The gonads develop from the urogenital ridges (Figure 67.2), which are formed during the fourth week of gestation by the proliferation of the coelomic epithelium and condensation of the underlying mesenchyme along the mesonephros. The germ cells located in the endoderm of the yolk sac migrate to the genital ridges. At the early stage of development, the gonad is bipotential, capable of forming into either a testis or ovary. During the sixth to seventh week of gestation, at least four different genes—Wilms' tumor suppressor gene (*WT-1*), Fushi–Tarza factor 1 (*FTZ-F1*), steroidogenic factor 1 (*SF-1*), and *LIM-1*—induce the development of the testis. The primordial germ cells differentiate into the Sertoli cells and associated Leydig cells, which aggregate into spermatogenic cords. Loose mesenchymal tissue condenses into a thick layer, the tunica albuginea, that surrounds the testis and separates it from the coelomic epithelium, thereby preventing further migration of mesonephric cells into the testis.

Classic teaching is that the female phenotype is the default developmental pathway in the absence of the *SRY* cascade. It is now known that at least one gene—dosage-sensitive sex reversal (*DAX-1*)—is essential for ovarian development. *DAX-1* is located on the short arm of the X chromosome. The gene products of *SRY* and *DAX-1* compete to stimulate the steroidogenic acute regulatory protein (StAR). The StAR protein is the first step in steroidogenesis, facilitating the conversion of cholesterol to pregnenolone (Figure 67.3). In the normal XY male, *SRY* overwhelms the one functional *DAX-1* gene, stimulating testicular development and subsequent testosterone production. In the normal XX female, two *DAX-1* genes are present without the competitive *SRY*, downregulating StAR and hence inhibiting testicular development, which results in ovarian development. In the fetal ovaries, the germ cells differentiate and are arrested in the last phase of meiotic prophase, forming the oocytes. The cells in the genital ridges develop into granulosa cells, which surround the oocytes and complete the formation of the ovaries.

Hormones

At 3.5 weeks' gestation, the Wolffian system appears as two longitudinal ducts connecting cranially to the

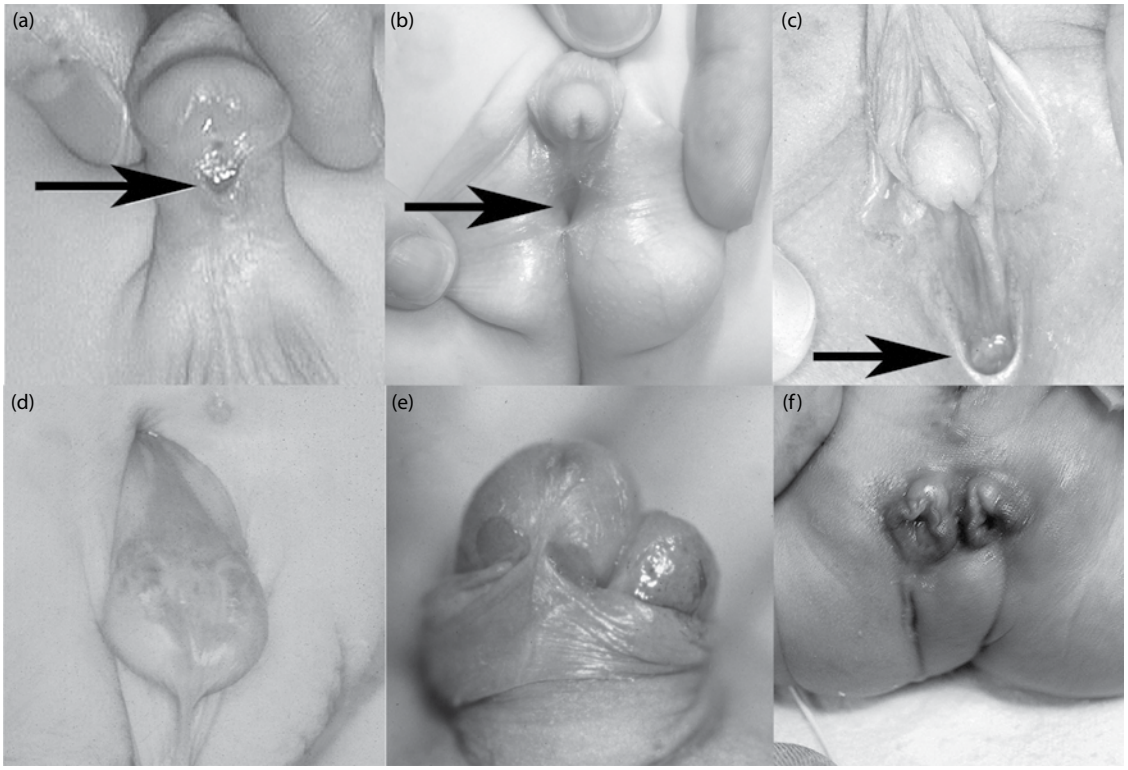

FIGURE 67.1 Genital abnormalities: (a) distal hypospadias, (b) scrotal hypospadias, (c) perineal hypospadias secondary to type 2 5α-reductase deficiency, (d) epispadias, (e) penile duplication anomaly, and (f) complete duplication of the female external genitalia.

mesonephros and caudually draining into the urogenital sinus (Figure 67.4). At approximately the sixth week of gestation, the Müllerian duct develops as an evagination in the coelomic epithelium just lateral to the Wolffian duct.

During the eighth to ninth week of gestation, Sertoli cells of the fetal testis secrete a glycoprotein, Müllerian inhibiting substance (MIS) or anti-Müllerian hormone. This protein induces the regression of the Müllerian ducts through the dissolution of the basement membrane and condensation of mesenchymal cells around the Müllerian duct. Because MIS acts locally, Müllerian duct regression occurs only on the ipsilateral side of the fetal testis, producing this hormone. MIS also induces the formation of seminiferous tubules and further differentiation of the testis. At the 9th or 10th week of gestation, the Leydig cells appear in the testis and begin to synthesize testosterone. This hormone transforms the Wolffian duct into the male genital tract, which is completed by the end of the 11th week of gestation.

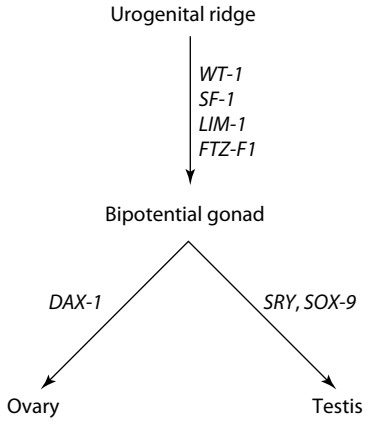

FIGURE 67.2 Sex-determining genes involved in testes and ovarian development.

Beginning in the ninth week of gestation, testosterone also induces the development of the external genitalia (Figure 67.5) from the genital tubercle, urogenital sinus, and genital swellings. At the molecular level, testosterone is converted to 5α-dihydrotestosterone (DHT) by the microsomal enzyme, type 2 5α-reductase, which is responsible for complete differentiation of the penis with a male-type urethra and glans. Testosterone dissociates from its carrier proteins in the plasma and enters cells via passive diffusion. Once in the cell, testosterone binds to the androgen receptor (AR) and induces changes in conformation, protecting it from degradation by proteolytic enzymes. This conformational change is also required for AR dimerization, DNA binding, and transcriptional activation, which are all necessary for testosterone to be expressed. Androgen binding also displaces heat shock proteins, possibly relieving constraints on receptor dimerization or DNA binding.

After entering the nucleus, the AR complex then binds androgen response element DNA regulatory sequences within the androgen-responsive genes and activates them. DHT also binds the AR, with greater androgenic activity than testosterone, in part because of its slow dissociation rate from the AR.

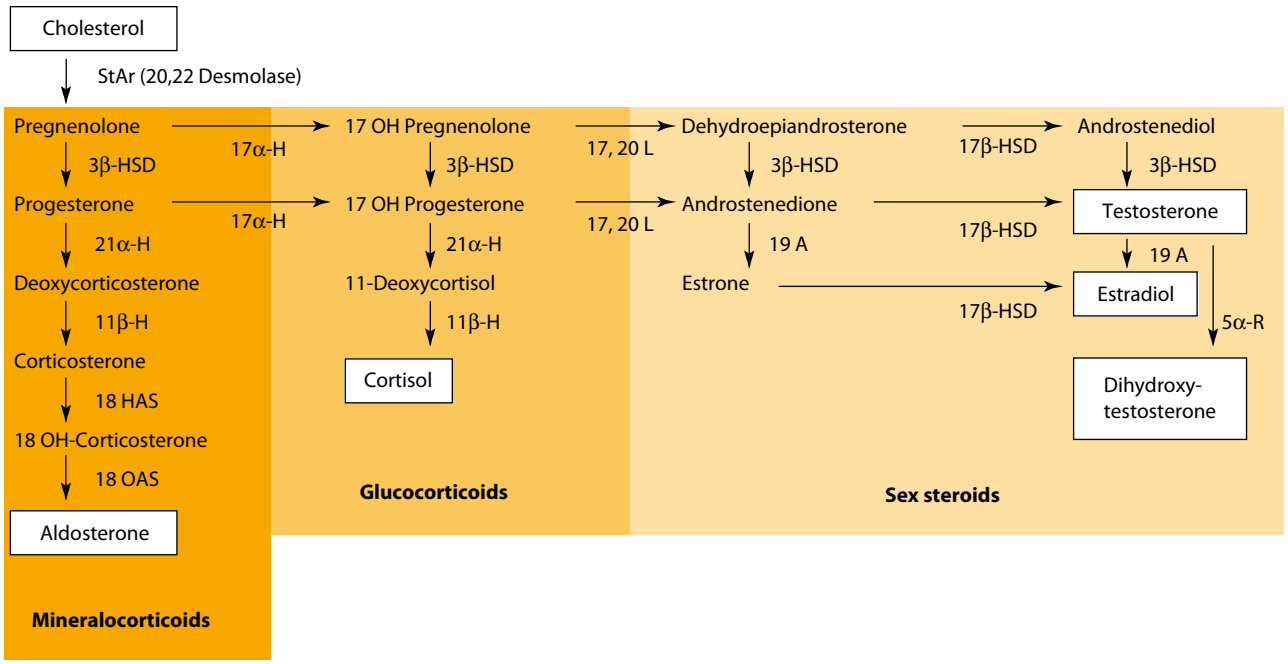

FIGURE 67.3 Pathway of steroid hormone biosynthesis and possible enzyme deficiencies. 3β-HSD = 3β-hydroxysteroid dehydrogenase; 17α-H = 17α-hydroxylase; 21α-H = 21α-hydroxylase; 11β-H = 11β-hydroxylase; 17, 20 L = 17,20-lyase; 17β-HSD = 17β-hydroxysteroid dehydrogenase; 18 HAS = 18-hydroxyaldosterone synthetase; 18 OAS = 18 oxidase-aldosterone synthetase, 5α-R = 5α-reductase; 19 A = 19-aromatase.

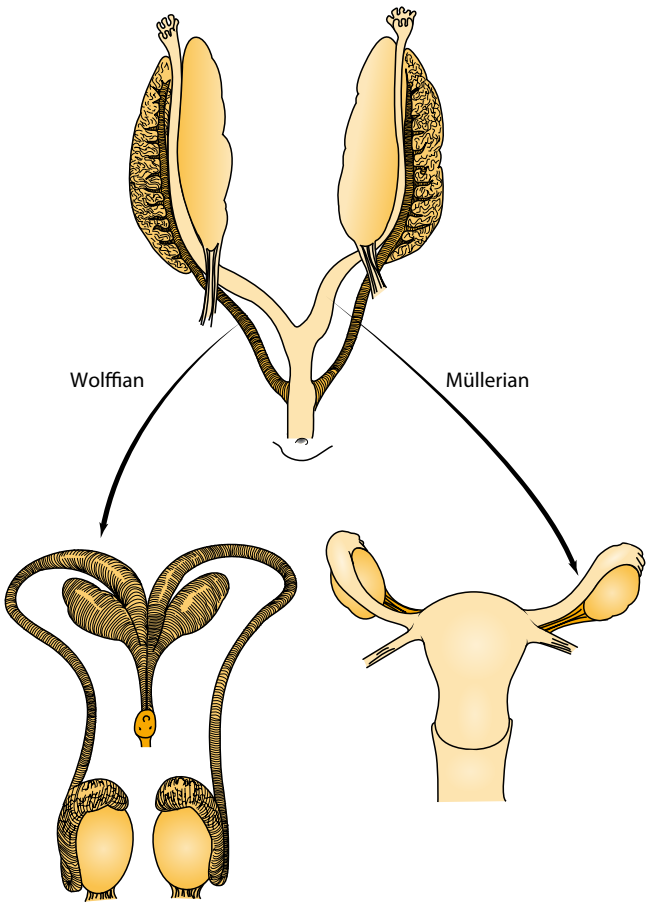

FIGURE 67.4 Schematic of male (Wolffian) and female (Müllerian) internal and external genital development from a common origin.

DHT then binds to nuclear receptors, forming a complex that regulates the transformation of these tissues into the glans penis, penile and cavernous urethra, Cowper's glands, prostate, and scrotum. At the 28th–37th week of gestation, testicular descent into the scrotum begins. Although its mechanism is not completely understood, it is clearly an androgen-dependent process.

The female internal genitalia develop from the Müllerian ducts. Without the hormones produced by the testis, the Wolffian ducts regress at the ninth week of gestation. At the same time, the Müllerian ducts begin to differentiate; the cranial portions form the fallopian tubes, while the caudal portions fuse to form the uterus, cervix, and upper portion of the vagina.

Concurrently, the external genitalia, defined as the lower portion of the vagina, the vestibule, Bartholin's and Skene's glands, the clitoris, and the labia minora and majora, develop from the urogenital sinus and genital tubercles. Like the testis, the ovary undergoes a partial transabdominal descent. However, transinguinal descent of the ovary does not occur, leaving the ovaries just below the rim of the true pelvis. The role of estrogen in the differentiation of the female phenotype is unclear.

EMBRYOLOGY: DEVELOPMENT OF THE MALE EXTERNAL UROGENITAL SYSTEM

Formation of the external male genitalia is a complex developmental process involving genetic programming, cell differentiation, hormonal signaling, enzyme activity,

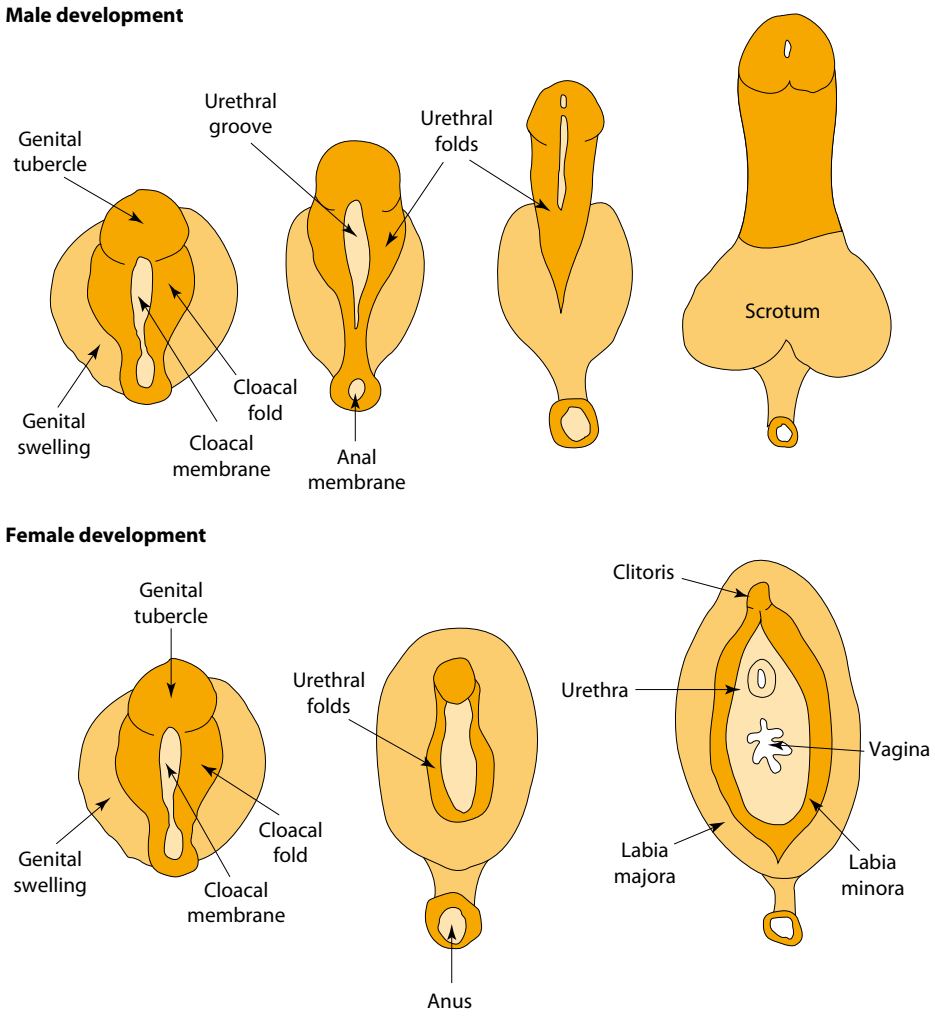

FIGURE 67.5 Differentiation of the male and female external genitalia from the indifferent stage to full differentiation (8–16 weeks).

and tissue remodeling.[4] By the end of the first month of gestation, the hindgut and future urogenital system reach the ventral surface of the embryo at the cloacal membrane.[5] The cloacal membrane divides the urorectal septum into a posterior, or anal, half and an anterior half, the urogenital membrane. Three protuberances appear around the latter. The most cephalad is the genital tubercle. The other two, the genital swellings, flank the urogenital membrane on each side. Up to this point, the male and female genitalia are indistinguishable. Under the influence of testosterone in response to a surge of luteinizing hormone from the pituitary, masculinization of the external genitalia takes place (Figure 67.5). One of the first signs of masculinization is an increase in the distance between the anus and the genital structures, followed by elongation of the phallus, formation of the penile urethra from the urethral groove, and development of the prepuce.[6,7] At 8 weeks' gestation the external genitalia remain in the indifferent stage (Figure 67.5). The urethral groove on the ventral surface of the phallus is between the paired urethral folds (Figure 67.6). The penile urethra forms as a result of fusion of the medial edges of the endodermal urethral folds.[8,9] The

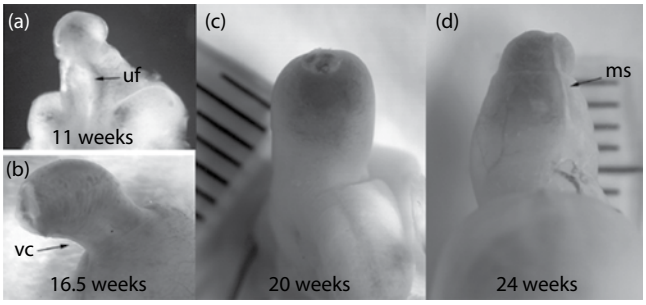

FIGURE 67.6 Male human fetal external genitalia during gestation. (a) At 11 weeks' gestation, note that the urethra is open and the urethral fold (uf) and groove are prominent in the transillumination view of the phallus. (b) At 16.5 weeks' gestation, note that the normal ventral curvature (vc) is shown, as well as the foreskin, which is almost completely formed. (c) At 20 weeks' gestation, penile and urethral development looks complete, with the prepuce covering the glans and the penile curvature resolving. (d) At 24 weeks, the prepuce covers the whole glans; note the midline seam (ms). Note the progression of natural curvature to a straight phallus during development.

ectodermal edges of the urethral groove fuse to form the median raphe. By 12 weeks, the coronal sulcus separates the glans from the shaft of the penis. The urethral folds have completely fused in the midline on the ventrum of the penile shaft. During the 16th week of gestation, the glandular urethra appears. The mechanism of the glandular urethral formation remains controversial. Evidence suggests two possible explanations: endodermal cellular differentiation or primary intrusion of the ectodermal tissue from the glans (Figure 67.7).

Anatomic and immunohistochemical studies advocate the new theory of endodermal differentiation, which shows that epithelium of the entire urethra is of urogenital sinus origin.[10] The entire male urethra, including the glandular urethra, is formed by dorsal growth of the urethral plate into the genital tubercle and ventral growth and fusion of the urethral folds. Under proper mesenchymal induction, urothelium has the ability to differentiate into a stratified squamous phenotype with characteristic keratin staining, thereby explaining the cell type of the glans penis.[11] There is no evidence of an ectodermal ingrowth, as was historically proposed (old theory).[12]

The future prepuce is forming at the same time as the urethra and is dependent on normal urethral development. At about 8 weeks' gestation, low preputial folds appear on both sides of the penile shaft, which join dorsally to form a flat ridge at the proximal edge of the corona. The ridge does not entirely encircle the glans because it is blocked on the ventrum by incomplete development of the glandular urethra. Thus, the preputial fold is transported distally by active growth of the mesenchyme between it and the glandular lamella. The process continues until the preputial fold (foreskin) covers all of the glans (Figure 67.6). The fusion is usually present at birth, but subsequent desquamation of the epithelial fusion allows the prepuce to retract. If the genital folds fail to fuse, the preputial tissues do not form ventrally; consequently, in hypospadias, preputial tissue is absent on the ventrum and is excessive dorsally.

GENITAL MALFORMATIONS

Unfortunately, to date there is no sound understanding of the etiology of genital anomalies and specifically hypospadias (which is the most common defect) that can inform primary prevention efforts and improve therapeutics. However, much is known about the genetics of hypospadias, hormone requirements for normal development, and environmental toxins, and a possible explanation for the increasing incidence of hypospadias that has already been noted.

Genetic Impairment

Uncertainty about the etiology of hypospadias is in part a reflection of the complicated and incompletely understood molecular and cellular basis for normal phallus and urethral development.[13] It is well established that the urethral folds fuse during the formation of the penile urethra in the 7th–12th week after ovulation.[4] Fusion of the folds eventually leads to a fully formed penis, a process that is dependent on the synthesis of testosterone by the fetal testis. Adequate virilization of the urogenital sinus and external genitalia during embryogenesis is also dependent on the conversion of testosterone to DHT by 5α-reductase.

Increasingly, researchers are examining the role of cellular signals other than testosterone and DHT in the morphogenesis of the phallus and the etiology of hypospadias. Normal embryogenesis of the urogenital system depends on epithelial–mesenchymal interactions, and it

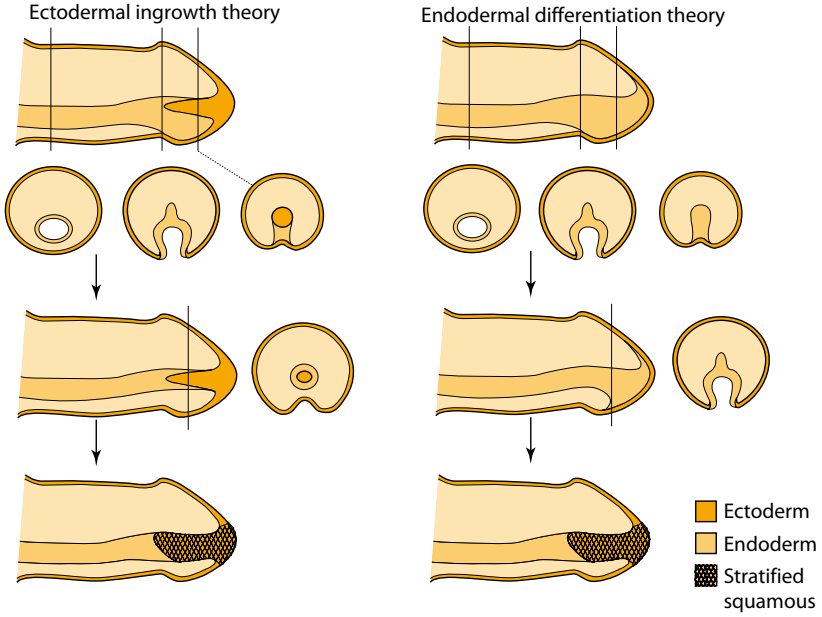

FIGURE 67.7 Theories of human penile urethral development. The ectodermal ingrowth theory, as described in most textbooks of embryology, postulates that the glandular urethra is formed by ingrowth of the epidermis. More recent data support the formation of the entire urethra via endodermal differentiation alone.

has been hypothesized that aberrant signaling between epithelium and mesenchyme could lead to hypospadias.[11] For example, prostate development requires "testosterone-dependent Sonic hedgehog (Shh) expression in the epithelium of the urogenital sinus."[14] In the mouse null for Shh, not only is penile development inhibited, but also there is a cloacal defect.[15,16] Mice null for fibroblast growth factor 10 have a proximal urethra opening and a flattened glans consistent with the hypospadias defect.[15] It is likely that researchers may find similar genetic, signaling molecules involved in epithelial–mesenchymal interactions in the phallus that play a role in its development.

Another area of investigation with respect to the etiology of hypospadias is the expression and regulation of homeobox (*Hox*) genes. These genes are transcriptional regulators that play an essential role in directing embryonic development. Genes of the *Hox A* and *Hox D* clusters are expressed in regionalized domains along the axis of the urogenital tract. Transgenic mice with loss of function of single *Hox A* or *Hox D* genes exhibit homeotic transformations and impaired morphogenesis of the urogenital tract.[17–20] Human males with hand–foot–genital (HFG) syndrome, an autosomal dominant disorder characterized by a mutation in *HOXA13*, exhibit hypospadias of variable severity, suggesting that *HOXA13* may be important in the normal patterning of the penis.[21–23] Furthermore, recent research has shown that the embryonic expression of certain *Hox* genes is regulated by hormonal factors.[24] Estrogen and the synthetic estrogen diethylstilbestrol (DES), for example, inhibit *HOXA9*, *HOXA10*, *HOXA11*, and *HOXA13* genes in mice. Thus, in addition to defects in *Hox* genes, it is possible that improper regulation or expression of hormonal factors during embryogenesis could disrupt normal expression of *Hox* genes and lead to reproductive tract anomalies.

Hormone Receptor Impairment

Studies examining the AR have yielded even less insight into the etiology of hypospadias. In fact, a number of studies have concluded that defects in the AR or mutations in the AR coding sequence are rare in patients with hypospadias.[25,26] In addition, Bentvelsen et al. measured AR expression in the foreskins of boys with hypospadias and age-matched controls and found no significant difference in mean AR content.[27]

Enzyme Impairment

Despite the central role that testosterone plays, attempts to ascribe all hypospadias to an underlying genetic defect in this pathway have only rarely been successful. Holmes et al. determined the incidence of defects in three major enzymes in the biosynthetic pathway of testosterone: 3β-hydroxysteroid dehydrogenase, 17α-hydroxylase, and 17,20-lyase (Figure 67.3). Morning fasting serum samples of pregnenolone, progesterone, 11-deoxycorticosterone, 17-hydroxypregnenolone, 17-hydroxyprogesterone, 11-deoxycortisol, cortisol, dehydroepiandrosterone (DHEA), androstenedione, androstenediol, testosterone, and DHT were obtained.[28] No significant differences in the androgen precursors and metabolites were found between the controls and the individuals with hypospadias. The response to adrenocorticotropic hormone (ACTH) was variable, without a significant difference between the patients with different degrees of hypospadias and/or published controls. These data indicate that enzymatic defects in the steroidogenic steps from cholesterol to DHT are not a frequent etiology of hypospadias.

Environmental Factors and Endocrine Disruptors

In the past, environmental factors were generally ruled out as causes for hypospadias.[29,30] More recently, multicausality models include environmental contaminants to determine the risk of developing a given phenotype. For example, familial clustering of hypospadias among first-degree relatives has been perceived as under the influence of a strong genetic and heritable component, but there have been many exceptions where genetics were ruled out. More recently, it has been suggested that environmental influences should be considered as well, taking into consideration that families share similar exposure: especially in those cases where the effects are the most profound, genetic predisposition exacerbated by environmental exposure should be considered.[31,32]

Attempts to determine risk factors for hypospadias have yielded a number of maternal and paternal risk factors. Among traditional studies of maternal risk factors for congenital anomalies, maternal age and primiparity are significantly associated with hypospadias, although some studies have contested the maternal age effect.[29] Paternal risk factors associated with hypospadias include abnormalities of the father's scrotum or testes[33] and low spermatozoa motility and abnormal sperm morphology.[31] It has been suggested that the recent increase in hypospadias reflects the improvement in fertility treatment, contributing to more subfertile men fathering children. As the authors state, this "relaxed-selection hypothesis, which states that there is a redistribution in the number of children born to fertile and infertile (subfertile) couples, may account for the increasing number of other defects and cancers of male genitalia observed today and the fall in sperm counts."[31]

In addition to parental risk factors, there is strong consensus in the literature that boys with hypospadias have lower birth weight.[34] Fredell et al. examined hypospadias in discordant monozygotic twins and found that the twin with hypospadias weighed 78% of the twin without hypospadias. The birth weight difference was still significant when compared with the birth weight difference between healthy monozygotic twins. Another study found that boys with hypospadias have a lower placental weight than control boys.[30] A 1995 meta-analysis of first-trimester exposure to progestins and oral contraceptives did not indicate an increased risk of hypospadias.[35] Exposure to DES was excluded in this study. However, a number of studies do list gestational exposure to progestins as a causal agent. Another recent study links a maternal vegetarian diet during pregnancy with an increase in the incidence of hypospadias.[36] This study looked at 51 boys with hypospadias from a group of 7928 boys born to mothers taking part in

the Avon Longitudinal Study of Pregnancy and Childhood (ALSPAC). The authors hypothesize that vegetarians have a greater exposure to phytoestrogens than omnivores. The phytoestrogens may come in the form of soy, which is high in isoflavones, or be related to endocrine disrupters in pesticides and fertilizers.[37] Whereas these risk factors do not reveal direct information about the etiology of hypospadias, they provide additional information that may reveal a common developmental pathway and can inform future research. For example, there is growing evidence that androgens play a central role in the lower birth weight of girls than boys.[38] They are also crucial to the development of the male reproductive tract; thus, perhaps exposure to an agent that compromises the weight-gaining advantage of an androgen during gestation could play a role in the development of hypospadias and lowered birth weight.

Increasing rates of hypospadias have paralleled reports of other untoward end points related to male reproductive health, including increases in testicular cancer,[39] increasing incidence of cryptorchidism, and decreasing semen and sperm quality.[40] In another study, 8% of patients diagnosed with undescended testes ($n = 252$) had urogenital anomalies and more than 50% of those had hypospadias.[41] The increasing incidence over the past 50 years of multiple end points, co-occurring with increasing production and use of synthetic chemicals, has raised concerns that environmental factors may play a role in the etiology of these problems.[32,42] It is now well documented, from wildlife studies and accompanying laboratory data, that a number of synthetic and natural chemicals commonly found in the environment can mimic or antagonize hormones or otherwise interfere with the development and function of the endocrine and reproductive systems.[43,44] Pregnant mice subjected to in utero exposure to both estrogen and prednisone have been shown to develop hypospadias.[45] Whether endocrine disruptors are having an impact on human male reproductive health and on hypospadias in particular is difficult to determine.[46] Regardless, public health agencies worldwide are increasingly concerned about endocrine disruption, and it remains an active area of research.[47–49]

GENETIC SUSCEPTIBILITY

A number of genes have been shown to infer an increased risk of hypospadias. For example, activating transcription factor (ATF3) and MAMLD1 (previously Cxorf6) are newly described candidate genes that are both associated with hypospadias.[50] ATF3 is an estrogen-responsive gene whose expression is increased in hypospadiac boys.[51,52] MAMLD1, which is expressed in the gonad during sex differentiation and interacts with steroidogenic factor 1, a transcription factor expressed in the mammalian sex-determining pathway, has also been shown to be mutated in patients with isolated hypospadias.[53] ZEB1, another estrogen-responsive gene, is overexpressed in penile skin in patients with severe hypospadias.[54] Genome-wide association studies have also shown that DGKK, which encodes diacylglycerol kinase κ, is strongly associated with hypospadias.[55] The implications of these studies is that in the future, it may be possible to predict genetic risk factors by identifying carriers of specific genetic polymorphisms.

EPIGENETIC CHANGES

Epigenetic changes may also be a possible mechanism explaining the etiology of hypospadias. Changes in DNA methylation level caused by either endogenous steroid hormones or exogenous endocrine disruptors may affect the expression of genes and, consequently, may contribute to abnormal male sexual differentiation and hypospadias. Epigenetic changes at the DNA level contribute to the control of transcription by both androgens and the AR. The first study supporting the role of DNA methylation as a possible cause of human hypospadias utilized high-throughput DNA methylation 450 K array-based assays.[56] Fourteen CpG sites were identified that were associated with hypospadias. These CpG sites were either in or near SCARB1, MYBPH, SORBS1, LAMA4, HOXD11, MYO1D, EGFL7, C10orf41, LMAN1L, and SULF1 genes. Two CpG sites in particular, SCARB1 and MYBPH, were highly associated with hypospadias.

ROLE OF ESTROGEN IN SEXUAL DIFFERENTIATION

While Alford Jost's theory of external genitalia development focusing exclusively on the presence or absence of androgen action is undoubtedly correct, it neglects the possibility of other endocrine mechanisms, such as estrogen action, and relegates female development as a default pathway.[57] Recent murine work has emphasized that normal female sex differentiation of the external genitalia is a uniquely active process and not simply a default pathway associated with the absence of androgen.[58–60] The presence of estrogen receptor α, estrogen receptor α, and aromatase in the developing external genitalia, as well as estrogen ligands in serum, when sex differentiation is occurring emphasizes the potential importance of estrogenic mechanisms during external genitalia development.[61] Finally, signaling via AR and ER can be antagonistic at cellular, tissue, and systemic levels, and thus the balance between AR and ER signaling may be critical in normal male and female development of the external genitalia.

CONCLUSION

Great strides have been made in understanding the molecular mechanism of genital formation. Understanding normal development is necessary to elucidate the etiology of abnormalities such as hypospadias. Recent work suggests that environmental exposure to endocrine disruptors may account for the increase in incidence of hypospadias cases. Prevention by reducing exposure may be the best strategy to reverse the increasing incidence of hypospadias.

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CHAPTER
68

Basic Science of the Testis*

Julia Spencer Barthold

INTRODUCTION

The testis is a highly complex organ with multiple interacting cell types that undergo rapid changes in the fetal, perinatal, and peripubertal male. The two main testicular compartments, the interstitium and the seminiferous tubules, respectively, reflect the two major functions of the testis: endocrine (hormone production) and exocrine (spermatogenesis). Several cell types exist in the interstitial space, including the hormone-producing Leydig cells, peritubular myoid (PTM) cells, peritubular nonmyoid cells, perivascular smooth muscle cells, and vascular endothelial cells. The tubules contain Sertoli cells and germ cells at various stages of development. After establishment of spermatogenesis, a blood–testis barrier (BTB) exists that separates the tubules into a basal compartment containing spermatogonia, leptotene, and preleptotene spermatocytes, and an adluminal compartment, containing meiotic spermatocytes, spermatids, and spermatozoa.

A coordinated program of fetal developmental signaling establishes an immature organ with full potential for fertility in adulthood; alterations in this program produce a spectrum of disease, ranging from subtle long-term deficiencies in testicular function to complete dysgenesis. Testicular hormones play key roles in the maturing testis and in the development and maintenance of reproductive tract structures and nonreproductive organs, such as brain and bone. Nontesticular hormones, growth factors, and microRNAs also impact testis development and function. This review summarizes our present knowledge of the key events in testis development and normal and abnormal testis function during the major periods of activity: fetal, neonatal, and pubertal.

Key areas that are reviewed in this chapter include

- Basic events in testis determination
- Patterning of testicular cords and establishment of cell types within the testis
- Establishment of the spermatogonial stem cell (SCC) niche and inhibition of meiosis
- Nuclear receptors and their ligands in the developing testis
- Fetal, neonatal, and pubertal activation of testicular hormone production and correlation with testis function
- Biology of the BTB and pathogenesis of germ cell injury

TESTIS DETERMINATION

Significant advances have been made in recent years that further elucidate mechanisms of testicular determination and will improve the diagnosis and treatment of children with disorders of sex development.[1–7] New insights from developmental studies in mice make clear that development of the indifferent gonad into a testis or ovary requires a balancing act of signaling pathways (Figure 68.1) that is triggered toward the male pathway by expression of *Sry* (sex-determining region on the Y chromosome).[6] Steroidogenic factor 1 (*Sf1*; now called *Nr5a1* based on updated nuclear receptor terminology) is expressed early in somatic (supporting and steroidogenic) cells and contributes to activation of *Sry*.[5] Other genes upstream of *Sry* discovered to date include *Wt1* (Wilms' tumor 1), *Lhx9*, *Cbx2*, *Gata4* and its cofactor *Fog2/Zfpm1*, *Pod1/Tcf21*, *Map3k4*, and several insulin receptors.[2,5] *Sry* expression is transient but in cooperation with *Sf1/Nr5a1* induces rapid and prolonged expression of another transcription factor, *Sox9* (SRY box-containing 9), in pre-Sertoli supporting cells.[2] The location and timing of *Sry* expression are critical for Sertoli cell specification and proliferation in mice; if inadequate or delayed, testis development fails or ovotestis formation occurs (Figure 68.2). As testis formation is triggered first in the midportion of the gonad, delay or deficiency that leads to ovotestis formation produces central testicular and polar ovarian differentiation.[3]

SOX9 upregulates its own expression and interacts with multiple other testis-determining molecules (Figure 68.1) that sustain and reinforce the male pathway and promote Sertoli cell proliferation via positive regulatory loops, including *Fgf9* (fibroblast growth factor 9), *Amh* (anti-Müllerian hormone), and *Ptgds* (prostaglandin synthase).[2] While important in male development, *Fgf9* and its receptor *Fgfr2* were also recently shown to play a key role in actively repressing the female-determining gene *Wnt4*, which, when expressed at endogenous levels in XX gonads, is sufficient to repress male development, supporting a mutual antagonism program during gonadal determination (Figure 68.1 inset).[8] Cell-specific gene expression studies in developing gonads confirm that the female program is dominant in pre-Sertoli progenitor cells and the male program, i.e., meiotic arrest, is the default in germ

* Standard vertebrate gene and protein symbol conventions are used throughout: italicized all uppercase (*HUMAN/PRIMATE*) and first letter only uppercase (*Mouse/Rat*) for *genes* and nonitalicized all uppercase for *proteins*.

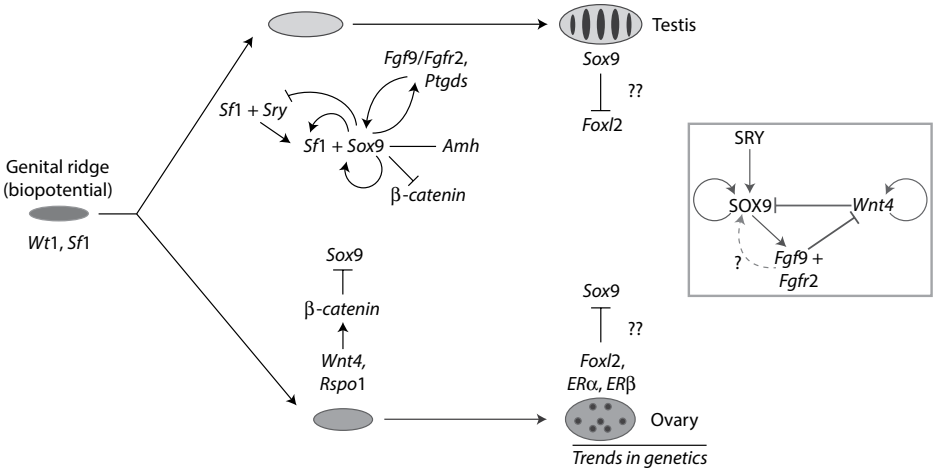

FIGURE 68.1 Molecular and genetic events in mammalian sex determination. The bipotential genital ridge is established by genes including *Sf1* and *Wt1*. In XY supporting cell precursors, increasing levels of SF1 activate *Sry* expression, and then SRY, together with SF1, boosts *Sox9* expression. Once SOX9 levels reach a critical threshold, several positive regulatory loops are initiated, including autoregulation of its own expression and formation of feed-forward loops via FGF9 or PGD2 (prostaglandin D2) signaling. If SRY activity is weak, low, or late, it fails to boost *Sox9* expression before β-catenin levels accumulate sufficiently to shut it down. SOX9 promotes the testis pathway, including *Amh* activation, and it also probably represses ovarian genes, including β-catenin and Foxl2. Inset: SOX9 upregulates *Fgf9* to repress *Wnt4*. In *Fgf9* or *Fgfr2* mutants, failure to repress *Wnt4* results in repression of SOX9 by *Wnt4* signaling and loss of male development. (From Sekido R, Lovell-Badge R. *Trends Genet* 2009;25(1):19–29. Inset: Jameson SA et al. *Dev Biol* 2012;370(1):24–32.)

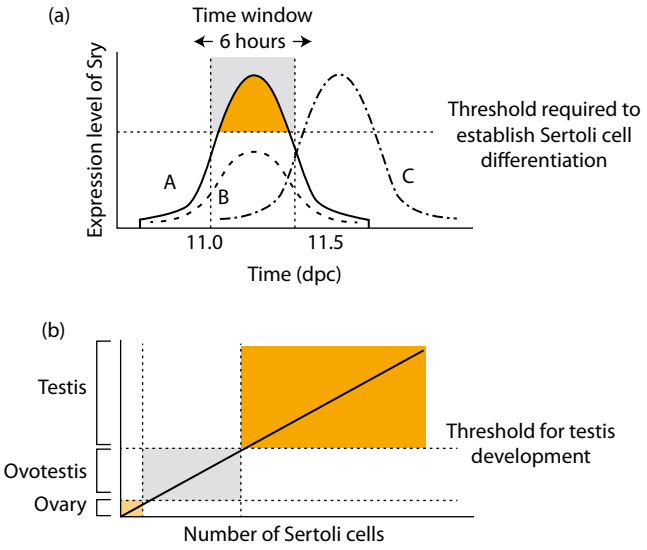

FIGURE 68.2 Two thresholds important for mouse sex determination. (a) *Sry* expression levels must exceed a certain threshold (blue) within a narrow time window (gray) in individual somatic gonadal cells of developing mouse gonads in order to induce Sertoli cell differentiation (curve A). If the level of *Sry* expression does not reach the threshold, as in WT1(+KTS)-null mice (curve B), or is delayed and misses the critical window, as in YDOM sex reversal (curve C), somatic gonadal cells fail to differentiate into Sertoli cells. (b) The number of supporting cell precursor cells that differentiate as pre-Sertoli cells must also reach a certain threshold level in order to induce testis formation (blue). In XXXY mouse chimera experiments in which the proportions of XY and XX cells making up an embryo vary, the gonad fails to form a testis if the number of Sertoli cells is below a threshold, resulting in the development of an ovotestis (gray) or an ovary (red). (From Kashimada K, Koopman P. *Development* 2010;137(23):3921–30.)

cells, with sex-specific repression of the alternative program required for cell fate commitment.[9]

In the human fetus, the indifferent gonadal ridge is established anterior to the mesonephros by postovulatory day 32, and expression of gonadal determination genes, such as *WT1* and *SF1* (*NR5A1*), is present.[10,11] *DAX1*, a dosage-sensitive nuclear receptor associated with male-to-female sex reversal and testicular dysgenesis with over- and underexpression, respectively, is also present in both sexes.[10] Expression of *SRY* transcripts commences after day 41 and peaks at day 44; however, unlike in the mouse fetus, *SRY* expression persists at low levels into at least the second trimester. *SOX9* expression peaks after day 44 and declines by day 52, at which time testis cords have formed.

TESTICULAR PATTERNING AND CELL-SPECIFIC DEVELOPMENT

Detailed information regarding how testicular organization occurs is emerging based on recent experiments in the fetal mouse. Patterning of the testis requires a temporal series of events (Figure 68.3):[3,4,6,7,12] (1) germ cell migration from the extraembryonic mesoderm to the genital ridge prior to gonad differentiation, (2) specification of Sertoli cell precursors arising from the coelomic surface epithelium of the genital ridge, (3) proliferation and migration of additional Sertoli and interstitial cell precursors from the coelomic epithelium, (4) migration of vascular endothelial and interstitial cells from the mesonephros near its border with the gonad, and (5) establishment of testicular cords and, in rodents, a prominent testicular vessel.[13] After specification of Sertoli cells, vascular endothelial cells migrate into the genital ridge

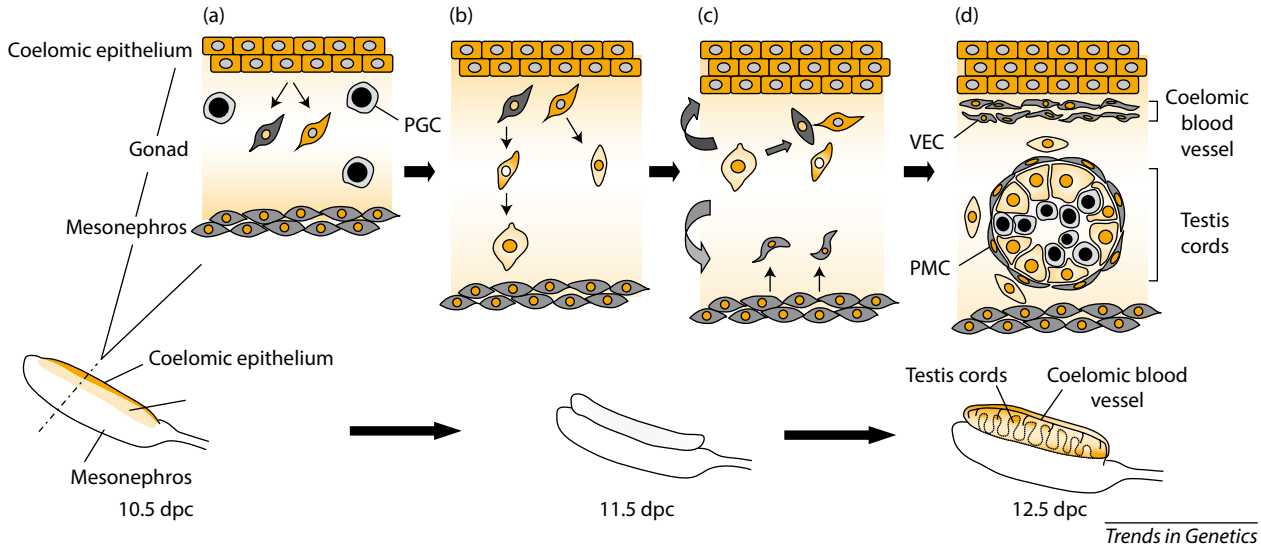

FIGURE 68.3 Cellular organization during testis development. (a) The testis arises from the genital ridge, a thickening under the coelomic epithelium (CE) adjacent to the mesonephros. PGCs (black) have migrated from the extraembryonic ectoderm by 10.5 days postcoitum (dpc); Sertoli (red) and Leydig (blue) cell precursors migrate from the CE. (b) With expression of SRY, *Sox9* is upregulated in Sertoli cells (yellow); *Sry* is then downregulated in SOX9-positive cells (green), and other CE cells give risk to interstitial (including Leydig) cells (pink). (c) Sertoli cells induce proliferation of CE cells (yellow arrows) and migration of mesonephric cells (purple arrow), which are primarily vascular endothelial cells (VEC) but also include Leydig and possibly PTM cells (PMC). (d) VECs help to partition the developing cords and form a characteristic ventral coelomic blood vessel. (From Sekido R, Lovell-Badge R. *Trends Genet* 2009;25(1):19–29.)

from the mesonephros and stimulate interstitial cell proliferation in response primarily to vascular endothelial growth factor A (VEGFA) (highly expressed in interstitial cells) and platelet-derived growth factor (PDGF) signaling, a process that drives testicular cord formation.[14] The mesenchyme expands along the developing vasculature to form partitions around existing Sertoli–germ cell clusters, although cords can still form in the absence of germ cells.[12] Sertoli cell signals that additionally appear to contribute to migration of mesonephric cells into the gonad include FGF9, AMH, transforming growth factor β (TGFβ), inhibin β B (INHBA) (also known as activin A), and neurotrophin 3.[5,12,15,16] In addition, secretion of extracellular matrix components by Sertoli and PTM cells contributes to organization of tubular architecture and requires direct physical interaction between the two cell types.[17]

In the developing human, testicular cords are established and the internal genitalia become nearly fully masculinized in the first trimester, and Leydig cell proliferation levels off after 15 weeks' gestation.[18] In contrast, Sertoli and germ cell proliferation continues, associated with increasing expression of conserved cell-specific transcripts, including *SOX9*, *FGF9*, *WT1*, *c-Kit*, and *KITL* (kit ligand), well into the second trimester.[18]

Sertoli Cells

Sufficient expansion in response to autoregulatory SOX9 signaling is required for adequate Sertoli cell function, which includes most notably AMH secretion and Müllerian duct regression in the first trimester in human fetuses. However, proliferation continues in a second wave that extends postnatally, which in humans ceases after the first year of life but resumes just prior to puberty.[19] Postnatal Sertoli cell proliferation correlates directly with spermatogenic capacity in adulthood and is enhanced by follicle-stimulating hormone (FSH),[19] autocrine expression of the chromatin remodeling protein ATRX (α-thalassemia/mental retardation X linked),[20] paracrine Inhba signaling by Leydig cells,[6] and androgen receptor (AR) signaling, probably via PTM cells.[21] Conversely, Sertoli cell proliferation is repressed by thyroid hormone (TH)[22] and nitric oxide (NO).[23] Immature Sertoli cells express AMH, aromatase, NCAM (neural cell adhesion molecule), and cytokeratin 18 and switch to WT1, GATA1 (GATA-binding factor 1), p27KIP1 (a cyclin-dependent kinase inhibitor [CDKI]), and AR expression during pubertal maturation.[19]

Multiple endocrine, paracrine, and autocrine pathways regulate Sertoli cell maturation (Figure 68.4) (reviewed in Tarulli et al.[24]). TH terminates proliferation and enhances maturation via regulation of CDKIs, including p27KIP1, which accounts for the excess testicular growth seen in neonatal hypothyroidism.[22] Additional factors required for Sertoli cell survival and maturation and consequent organization of testis cords include *Dicer*, encoding an enzyme that processes microRNAs, which regulate gene expression,[25] and *Dmrt1* (*doublesex*- and *mab-3*-related transcription factor), encoding a DNA-binding protein that is a conserved regulator of postnatal testis differentiation.[26]

Activin A (encoded by the *Inhba* gene), a developmental protein of the TGFβ superfamily produced by Leydig cells, is a key paracrine regulator of Sertoli cell proliferation via interactions with downstream SMAD proteins.[27] Activin A dosage defines the balance between Sertoli and germ cell proliferation and the ultimate Sertoli–germ cell ratio,[28] while SMAD3 dosage fine-tunes the balance of

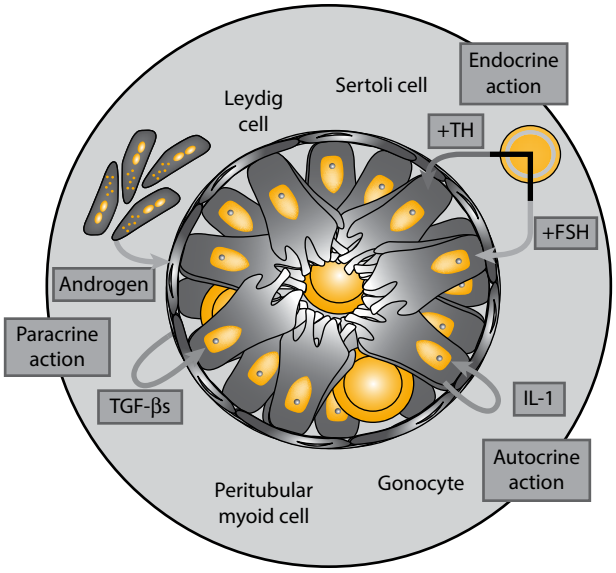

FIGURE 68.4 Major factors regulating Sertoli cell maturation in the pre- and postpubertal testis. Pubertal Sertoli cell proliferation is regulated by numerous endocrine (FSH and TH), paracrine (TGFβ and androgen), and autocrine (IL-1) factors that exert positive (green arrows) and negative (red arrows) effects. The balance of these factors, with their combined effect on specific cell cycle regulators, determines the size of the adult Sertoli cell population. The establishment of a high Sertoli cell number is central to maximal fertility in adulthood. (From Tarulli GA et al. *Biol Reprod* 2012;87(1):13, 1–11.)

proliferation versus maturation of Sertoli cells via regulation of AR expression.[29]

Interstitial Cells

The interstitial compartment of the fetal testis contains a number of cell types, including Leydig and PTM cell precursors, vascular endothelial cells, and unidentified mesenchymal cells. Many of these cells originate as coelomic epithelial cells that undergo epithelial-to-mesenchymal transition and proliferate.[12,30] Mesonephric cell migration also contributes to the interstitial compartment, with the primary, if not exclusive, migrating cell type initially thought to be endothelial.[13] However, recent experiments in which physical separation of the genital ridge and mesonephros was avoided showed that Leydig and potentially other interstitial cell precursors clearly do migrate from the adjacent mesonephros into the gonad along existing perivascular pathways.[31]

Leydig Cells

The identification of two distinct sources of progenitor Leydig cells is of potential importance considering that heterogeneous populations occur postnatally. In humans, *fetal Leydig cells* become active at 6–7 weeks' gestation; proliferate, differentiate, and mature between 8 and 18 weeks; and involute after 24 weeks.[32,33] Sertoli cell–secreted paracrine factors that contribute to Leydig cell differentiation include desert hedgehog (DHH) and PDGFs.[34,35] Interstitial autocrine factors that support Leydig cell differentiation and survival include the transcription factors GATA4 and ARX (aristaless-related homeobox), insulin-like growth factors (IGFs), the nuclear receptor COUP-TFII (NR2F2), TGFBR3 (TGFB receptor 3 or β-glycan), and hepatocyte growth factor (HGF).[36–39] In contrast, Notch signaling promotes interstitial progenitor cell maintenance and inhibits Leydig cell differentiation.[40]

After birth, a *neonatal Leydig cell* population emerges that likely includes differentiating interstitial precursors.[39,41] After transient activation of the hypothalamic–pituitary–gonadal (HPG) axis (see below), these cells either degenerate or regress to form small, *immature Leydig cells* that may persist during childhood and, along with stem cell precursors, contribute to a distinct *adult Leydig cell* population.[41] The progenitor Leydig cells that contribute to later waves of development at puberty may originate from peritubular and/or perivascular mesenchymal precursors, but their ontogeny is not defined.[31,42,43]

Peritubular Myoid Cells

The PTM cell forms a subset of the interstitial population that is unique to the male gonad. PTM cells participate in formation of the testicular cords; form a distinctive, elongated cell layer surrounding the tubules; and in adulthood, participate in contractile function of the seminiferous tubules.[44] They are one of two peritubular cell subtypes, myoid and nonmyoid,[45] the latter being potential Leydig cell precursors. No early specific marker that defines the origin of the myoid population exists, since most proteins expressed in PTM cells are also expressed in other interstitial cells.[46] However, smooth muscle α-actin, initially present in both gonadal interstitial and mesonephric cells, becomes specifically localized in PTM cells by late gestation.[30] In addition to the role of PDGF signaling in interstitial cell proliferation during testis determination, PTM cells continue to express PDGF receptors,[47] which may in part mediate postnatal testicular growth.[48]

Two Sertoli cell signals, DHH and DAX1 (dosage-sensitive sex reversal, adrenal hypoplasia critical region on chromosome X, 1), participate in PTM cell differentiation and organization in mice and are required for correct cord formation.[49,50] Similarly, the ARX protein required for Leydig cell differentiation is expressed in interstitial (including PTM) but not Leydig cells,[36] reinforcing the importance of cell–cell signaling in testis development. Other types of paracrine signaling between PTM and Sertoli and/or Leydig cells is also likely but not well characterized, particularly in fetal life, but androgen signaling may be a major component since AR expression is consistently present in these cells beginning in the fetus (see below).

Germ Cells

Primordial germ cells (PGCs) are specified by the extraembryonic ectoderm via bone morphogenetic protein (BMP) signaling to pluripotent epiblast cells in mammalian fetuses.[51] They then migrate from the primitive streak to the future hindgut in response to signaling via the c-Kit receptor tyrosine kinase and its ligand, stem cell factor

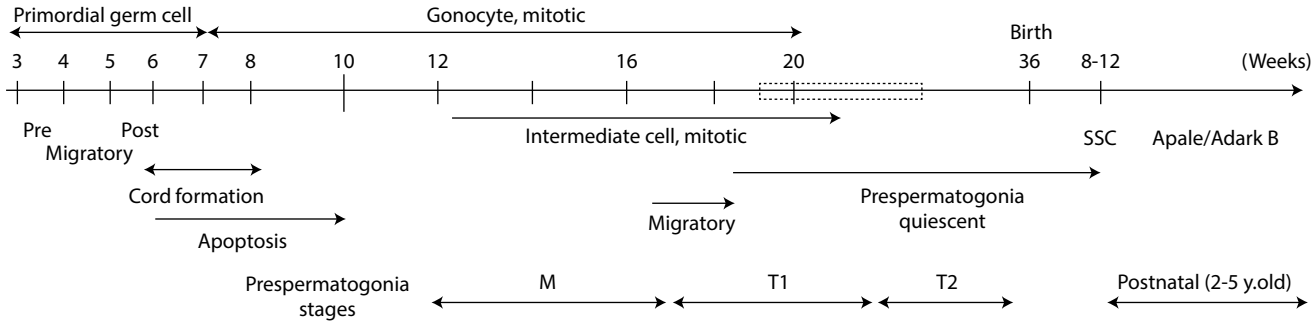

FIGURE 68.5 Schematic representation of the timeline of human gonocyte development. Apale/Adark/B, stages of spermatogonial development; M, mitotic; T1, transitional 1; T2, transitional 2. The box indicates the period between gestation weeks 19 and 25, at which time a progressive shift occurs between OCT4 and MAGE-A4 expression in the germ cell. (From Culty M. *Birth Defects Res C Embryo Today* 2009;87(1):1–26.)

(SCF) (or kit ligand [KITL]),[51] and in human fetuses arrive by the sixth week and become localized within the testicular cords by the eighth week of gestation (Figure 68.5).[52] Prior to the end of the first trimester of gestation, subpopulations of both proliferating and degenerating germ cells exist. By the second trimester, three subpopulations of germ cells—gonocytes, intermediate spermatogonia, and prespermatogonia (also called prospermatogonia)—are distinguishable by loss of POU5F1 (POU domain class 5 homeobox 1, also known as OCT4) and c-Kit and gain of MAGE-A4 (melanoma antigen, family A, 4) immunopositivity with developmental stage.[53] By the 20th week (Figure 68.5), gonocytes are no longer present and prespermatogonia evolve as M (mitotically active), T1 (quiescent), and T2 (resuming mitosis) cells.[52,53] Both differentiation and apoptosis (programmed cell death) occur in phases during development of human germ cells, as well as of Sertoli and Leydig cells, and have important roles in establishing a normal cellular population in the testis.[54]

The postnatal period is a critical developmental window for germ cells as prespermatogonia (still called gonocytes in neonatal rodents) proliferate and migrate to the tubular basement membrane or undergo apoptosis.[55] Failed migration leads to excess apoptosis and possibly to persistence of abnormal undifferentiated cells that may predispose to future malignant transformation.[52] After migration, prespermatogonia become undifferentiated type A spermatogonia; in humans and primates, this includes types Ad and Ap spermatogonia,[56] and a subset of these become the population of SSCs.[57] Type Ad are presumed to be resting and Ap to be active SSCs because the conserved stem cell markers GFRA1 (glial cell–derived neurotrophic factor [GDNF] receptor α1) and PLZF (promyelocytic leukemia zinc finger protein, now known as ZBTB16, zinc finger, and BTB domain–containing protein 16) are expressed in most Ad and about half of Ap spermatogonia, while progenitor-specific NGN3 (neurogenin 3) expression is acquired in a subset of Ap spermatogonia.[56] Progenitor type A spermatogonia differentiate into c-Kit-positive type B spermatogonia, which appear by 5 years of age.[56,58]

Sertoli cells provide critical physical support and orchestrate creation of a microenvironment for SSCs at the tubular basement membrane.[59,60] Proper establishment of this SSC niche is critical for future germ cell differentiation and for the SSC self-renewal that occurs through life. Sertoli cells are stimulated by FSH, growth factors, and cytokines and in turn produce factors such as GDNF, KITL, ETV5, and SIN3A that promote stem cell renewal within this niche.[59,61] GDNF signaling is dose dependent in that high levels promote SSC self-renewal, while low levels promote SSC differentiation.[52] Sertoli cell proliferation also occurs in this time-frame and is a key element in determining the adequacy of the SSC niche.[62] Sertoli cells can also indirectly influence SSC self-renewal by inducing Leydig and PTM cells to secrete factors such as CSF1 (colony-stimulating factor).[63] In fact, SSCs may preferentially locate adjacent to interstitial areas rich in vasculature and Leydig cells.[64]

Factors that directly or indirectly regulate migration of prespermatogonia to the basement membrane and/or proliferation are incompletely characterized but are known to include PDGF, c-Kit, estrogens, TH, and proteins involved in cellular adhesion.[52,55,60,65–67] Although expressed in Sertoli cells and required for their maturation and support of the germ cell population, recent work suggests that conditional deletion of *Dmrt1* in germ cells specifically prevents their radial migration to the basement membrane.[26] In human males, neonatal migration and proliferation of prespermatogonia coincides with activation of the HPG axis, which occurs in the first few months of life (see below). While FSH-regulated secretion of growth factors by Sertoli cells is important in establishing the SSC niche, a role for luteinizing hormone (LH) or testosterone in gonocyte migration or proliferation has not been identified and, at least in the fetal mouse, androgen action correlates with inhibition of gonocyte proliferation.[52] In addition, tubules contain adluminal spermatogonia and degenerating cells throughout childhood, suggesting that population renewal continues to occur without significant hormonal stimulation.[58]

Meiosis begins in female germ cells prenatally, but in males is largely suppressed until puberty, although prepubertal testes contain occasional spermatocytes. Retinoic acid (RA) induction of *Stra8* (stimulated by RA gene 8) appears to be the primary trigger for meiotic entry.[68,69] In males, the RA-metabolizing enzyme CYP26B1 was considered primarily responsible for the inhibition of meiosis. However, recent evidence in mice suggests that other male-specific factors act to prevent meiosis in male germ

cells,[70] and interestingly, these appear to include DMRT1 and TGFβ proteins,[71–74] which also have key roles in other aspects of testis development. Similar to upstream factors like SOX9, which both reinforce the male pathway and inhibit female development, these proteins activate markers of spermatogonial differentiation (*Sohlh1/2*, *Nanos2*, and *Dnmt3l*) while blocking female-specific (*Foxl2*) gene expression in somatic cells. Interesting, recent data indicate that human carcinoma in situ (CIS) cells can simultaneously express meiosis-inducing and meiosis-inhibiting regulatory proteins, supporting the hypothesis that they are dysregulated persistent gonocytes.[75]

Major advances in basic research in recent years have improved understanding of testicular developmental mechanisms. It is increasingly evident that key participants, including DMRT1, PDGF, and TGF (including TGFβ, BMPs, AMH, activin, and GDNF) proteins, activate signaling pathways in multiple cell types and are pivotal in cell-specific testis development. For many of these pathways, there is strong evidence for mammalian conservation. Although some differences exist, many meiotic and spermatogonial markers identified in mice are also expressed in the human fetal testis.[76] Overlap in SSC-specific mRNAs found in man and mouse also suggests mammalian conservation in regulation of the germ cell niche, particularly with regard to expression of GDNF pathway genes involved in SSC self-renewal.[77] This increased knowledge of the biology of germ cell development has the potential to impact fertility potential and outcomes. For example, potential SCC isolation, identification, and expansion in long-term culture or cryopreservation may create future possibilities for stem cell transplantation[78–80] and allow fertility preservation in males undergoing gonadotoxic therapy for cancer.[81] In addition, recent evidence suggests a direct relationship between epigenetic modifications in sperm and expression of developmental genes in offspring, which may improve our understanding of the etiology of birth defects.[82]

NUCLEAR RECEPTORS IN THE TESTIS

Nuclear receptors, particularly the steroid androgen and estrogen receptors, are expressed in testicular cells and are particularly important in Leydig cell differentiation and function,[83] but also play key roles in other testicular cell types (Table 68.1). However, their physiologic role in testis and relevance to human disease is not always clear, since expression and function may differ with species and developmental stage. Receptors of particular clinical relevance during development include an AR (NR3C4), estrogen receptors ERα (NR3A1) and ERβ (NR3A2), SF1 (NR5A1), and DAX1 (NR0B1). SF1 and DAX1 are key regulators of somatic and tubular development; mutations of either *NR5A1* or *NR0B1* are associated with hormonal insufficiencies of adrenal and testis and testicular dysgenesis.[50,84] Androgen and estrogen receptors are of interest as potential targets of exogenous agents that are considered endocrine disruptors.[85,86] Androgens and estrogens also signal through nonclassical receptors located in the cytoplasm or at the plasma membrane, but a role for such signaling in testis development or function remains undefined.

Despite interspecies differences, PTM and other interstitial cells, including some Leydig cells, most consistently express AR in the fetus and prepubertal male,[87,88] and human fetal PTM cells expand in culture medium containing dihydrotestosterone (DHT).[89] Lack of AR expression in the immature Sertoli cell explains why initiation of spermatogenesis does not occur with increased androgen production in the fetal and postnatal periods.[90,91] Developmental acquisition of AR expression in Sertoli and Leydig cells allows androgen-regulated processes to proceed normally at puberty, including establishment of the adult Leydig cell population, repression of AMH expression, meiotic entry, establishment of the BTB, and support of spermatogenesis.[83,92]

Estrogens signal through two classic nuclear receptors, ERα and ERβ. In addition, the androgen 5α-androstane-3β,17β-diol (3β-diol), a metabolite of DHT, is a known alternative ERβ ligand.[93] Studies of ERKO (ERα knockout) mice suggest that estrogenic suppression of steroidogenesis and INSL3 is mediated by ERα,[83] but human studies suggest little, if any, expression of ERα in fetal,[53,88] postnatal,[87] or adult[94] testes, although ERα expression is reported in postnatal germ cells.[95] In contrast, ERβ is expressed in Leydig, PTM, Sertoli, and germ cells at all time points[53,87,88,94] and may mediate what appears to be the main effect of estrogen signaling in testis: stimulatory effects of estradiol and 3β-diol on germ cell proliferation and maturation.[66,93,94] Local conversion of testosterone to estradiol by aromatase is possible in the testis because Leydig, Sertoli, and some germ cells express this enzyme.[94]

Differences between species with regard to AR and ER localization and their potential role in mediating the effects of endocrine-disrupting (antiandrogenic and estrogenic) compounds provide uncertainty about the relevance of these agents to human health.[85] Therefore, newer efforts are directed at determining the specific response of human testis, either in culture or via xenografting into nude mouse recipients, potentially a more physiologic approach.[85] Available data suggest species differences not only between man and rodent but also between mouse and rat. For example, while similarly susceptible to germ cell toxicity, xenotransplanted human fetal and mouse testes are resistant to the phthalate-induced inhibition of steroidogenesis seen in rats.[96–98] In contrast, cultured human testes are more sensitive than rodent testes to the inhibitory effects of bisphenol A (BPA) on testosterone production and *INSL3* expression.[99]

HORMONAL ACTIVITY AND TESTICULAR FUNCTION

Three phases of testicular hormone activation occur in normal humans (Figure 68.6): the first trimester of gestation, the neonatal period, and puberty. These are necessary for masculinization of the male reproductive tract and brain and for activation and support of the developmental program of the testis. Circulating hormones of major importance during this period include human chorionic gonadotropin (hCG) produced by the placenta,

TABLE 68.1 Cell-specific functions of selected nuclear receptor (NR) proteins in testis

NR nomenclature	Mouse gene name	Common name/symbol	Target cell	Function based on available data
NR1A1, NR1A2	*Thra*, *Thrb*	Thyroid hormone receptor/TRα, TRβ	LC	Stimulates postnatal differentiation and steroidogenesis
			SC	Represses proliferation and enhances maturation[146]
			GC	Indirectly promotes gonocyte migration[55]
NR1B1, NR1B2, NR1B3	*Rara*, *Rarb*, *Rarc*	Retinoic acid receptor/RARα, RARβ, RARγ	LC	Stimulates fetal steroidogenesis
			GC	Meiosis initiation[68,69]
NR1C1, NR1C2, NR1C3	*Ppara*, *Ppard*, *Pparg*	Peroxisome proliferator-activated receptor/PPARα, PPARβ/δ, PPARγ	LC	Represses steroidogenesis
			SC, GC	Lipid metabolism
NR2F2	*Nr2f2*	Chicken ovalbumin upstream promoter-transcription factor II/ COUP-TFII	LC	Stimulates formation of progenitor cells and Leydig cell maturation
NR3A1	*Esr1*	Estrogen receptor α/ERα	LC	Represses fetal differentiation, steroidogenesis, and *Insl3* expression in mice; not expressed in humans
			SC	Stimulates peripubertal proliferation[147]
NR3A2	*Esr2*	Estrogen receptor β/ERβ	LC	Represses proliferation, stimulates steroidogenesis in adult LCs
			SC	Stimulates peripubertal proliferation[147]
			GC	Represses gonocyte proliferation[86]
NR3C1	*Nr3c1*	Glucocorticoid receptor/GR	LC	Represses steroidogenesis; apoptosis of adult LCs
NR3C4	*Ar*	Androgen receptor/AR	LC	Development/maturation of adult LCs
			SC	Proliferation, formation of the BTB, meiosis progression, support of spermatogenesis[148,149]
			PTM	Differentiation,[150] proliferation,[89] indirect effect on development/maturation of adult LCs[151]
NR4A1	*Nr4a1*	Nerve growth factor induced-B/ NGFI-B, NUR-77	LC	Stimulates steroidogenesis and *Insl3* expression in cell lines, repressed by NR3C1
NR5A1	*Nr5a1*	Steroidogenic factor 1/SF1	LC	Stimulates fetal differentiation, steroidogenesis, and *Insl3* expression
			SC	Stimulates maturation[152]
NR5A2	*Nr5a2*	Liver receptor homolog 1/LRH1, FTF	LC	Stimulates steroidogenesis
			SC, GC	Expression dependent on differentiation state and heat exposure[153]
NR0B1	*Nr0b1*	Dosage-sensitive sex reversal, adrenal hypoplasia critical region on chromosome X, 1/DAX1	LC	Stimulates migration during testis determination;[50] represses adult LC steroidogenesis via altered *Nr4a1*, *Nr5a1*, and aromatase expression
			SC	Stimulates survival and differentiation[154]
			PTM	Indirectly stimulates differentiation[50]

Source: Data for Leydig cells from Martin LJ, Tremblay JJ. *Biol Reprod* 2010;83(1):3–14. Additional data as referenced.
Abbreviations: LC, Leydig cells; SC, Sertoli cells; GC, germ cells; PTM, peritubular myoid cells.

LH and FSH by the pituitary, AMH and inhibin B by Sertoli cells, and androgens (including testosterone) and INSL3 by Leydig cells.

Fetus

During fetal life, testicular hormones promote masculinization via testosterone and DHT, Müllerian duct regression via AMH, and testicular descent via INSL3 and testosterone. Soon after their differentiation, Sertoli cells begin AMH secretion, which persists at high levels well into the third trimester[21] and remains detectable in cord blood.[100] Inhibin B levels are also elevated in male fetuses in the last half of gestation and much higher than those observed in females.[101] Testosterone is initially produced at about 8 weeks' gestation in the human fetus, and levels in amniotic fluid and testis peak at 12–14 weeks.[85] INSL3 levels in amniotic fluid also appear to peak in this time frame,[102] and *INSL3* mRNA is measurable at 12 weeks' gestation,[18] but protein levels have not been measured in first-trimester fetuses.

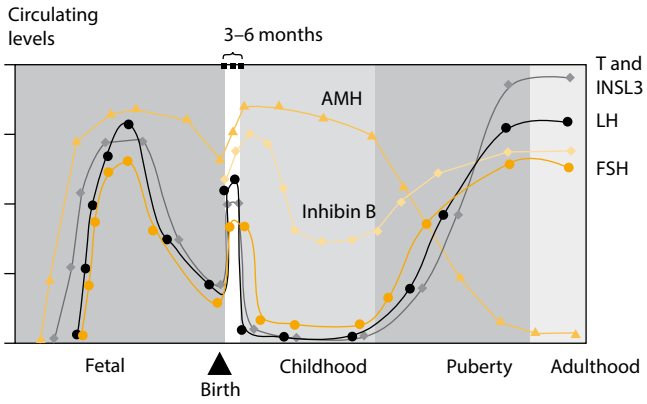

FIGURE 68.6 HPG axis activation in males. Schematic ontogeny of circulating levels of LH, FSH, testosterone (T), insulin-like 3 (INSL3), anti-Müllerian (AMH), and inhibin B in males from conception until adulthood. (From Grinspon RP et al. *J Pediatr Endocrinol Metab* 2012;25(1–2):3–11.)

Initial testosterone production may be independent of pituitary hormones in human fetuses, as it is in rodents.[85] Nonetheless, the subsequent peak in production is most likely regulated primarily by hCG or LH, since by 10 weeks' gestation hCG levels are peaking and LHCGR (LH/hCG receptor) and fetal LH are measurable in testis and amniotic fluid, respectively (Figure 68.6).[85] Moreover, complete feminization and Leydig cell agenesis occur in males with inactivating mutations of *LHCGR*.[103] Peak production and subsequent waning of fetal hormone production by Leydig cells coincide with their maximal proliferation[18] and subsequent involution, respectively, by the end of the second trimester. Unlike testosterone production, which is acutely responsive to gonadotropin stimulation, *INSL3* expression appears to be largely constitutive, as levels in older males do not respond to gonadotropin stimulation.[102]

Interestingly, recent studies have shown an alternative "backdoor" androgen biosynthesis pathway that exists in the developing testis of tammar wallaby and mouse that leads to the local production of DHT[104] (Figure 68.7). In this pathway, enzymes in the aldo-keto reductase (AKR1C) family synthesize 5α-androstane-3α,17β-diol (androstanediol or 3α-androstanediol) from progesterone and convert it to DHT, bypassing testosterone formation. This pathway is also active in human fetal testis, since individuals with mutations in two enzymes in this pathway, *AKR1C2* and *AKR1C4*, are feminized.

Neonate

A second key period of pituitary and testicular hormone activation occurs in the first 3 months of life, often referred to as "mini-puberty" in males (Figure 68.6). During this

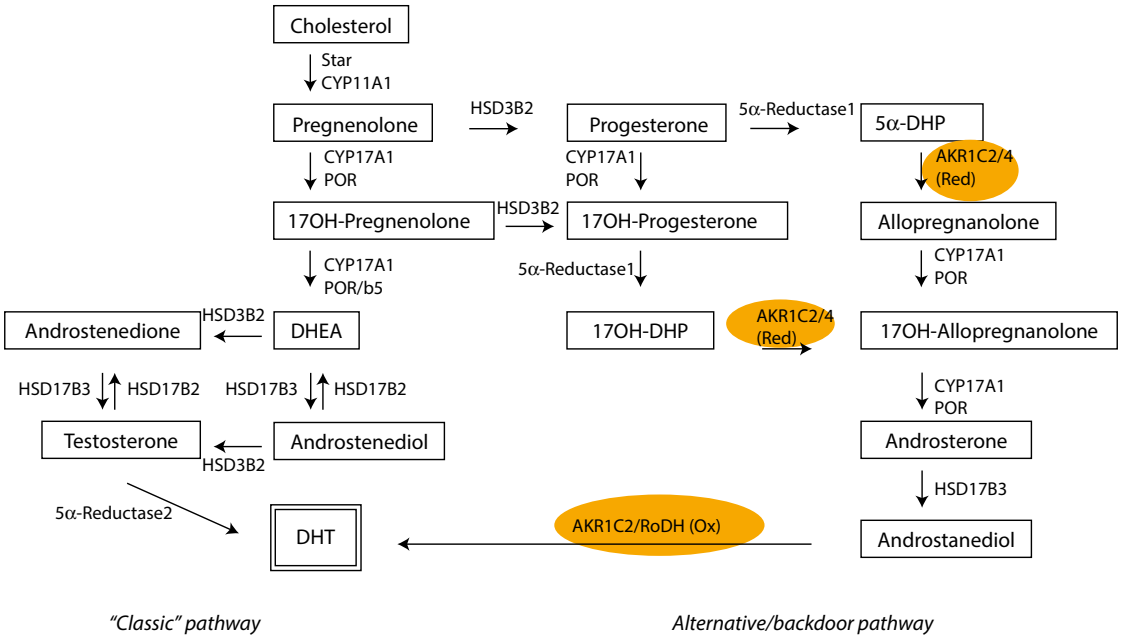

FIGURE 68.7 Synthesis of DHT via the classic and alternative (backdoor) pathways. The *classic pathway* of steroidogenesis (left) includes CYP11A1 (cholesterol side-chain cleavage enzyme, P450scc), StAR (steroidogenic acute regulatory protein), CYP17A1 (17α-hydroxylase/17,20-lyase, P450c17), POR (cytochrome P450 oxidoreductase), HSD3B2 (3β-hydroxysteroid dehydrogenase, type 2), HSD17B3 (17β-hydroxysteroid dehydrogenase, type 3), and 5α-reductase, type 2 (encoded by SRD5A2). The *alternative pathway* is characterized by the presence of additional enzymes: 5α-reductase, type 1 (5α-reductase 1, encoded by SRD5A1), AKR1C enzymes, and RoDH (3-hydroxyepimerase, encoded by HSD17B6). 17OH-allo-pregnanolone (5α-pregnan-3α,17α-diol-20-one or Pdiol) is a key intermediate in this pathway.[104] While the reaction between DHT and 3α-androstanediol (3α-diol) is reversible, DHT is also irreversibly converted to 5α-androstane-3β,17β-diol (3β-androstanediol or 3β-diol), an estrogen receptor β ligand (not shown). (From Fluck CE et al. *Am J Hum Genet* 2011;89(2):201–18.)

time frame, levels of serum LH and FSH surge as early as the first week of life, followed by increases in testosterone, AMH, and inhibin B, while INSL3 levels are high in both cord blood and at 3 months of age.[100,105–108] Evidence from individuals with androgen insensitivity suggests that the postnatal hormone surge is related to the effects of postdelivery androgen withdrawal, with reflex increases in hypothalamic and pituitary activity.[109]

Postnatal maturation and stabilization of the testis and male reproductive tract, respectively, are presumed consequences of the neonatal hormone surge.[109] Data from a recent longitudinal study suggest that the gonadotropin and testosterone surge actually occurs at 1 month of age and is more pronounced in preterm boys.[110] In this series, the percentage growth of the neonatal testis and penis was positively correlated with levels of LH, FSH, and testosterone. The proposal that neonatal testis growth is likely due to seminiferous tubule elongation in response to Sertoli cell proliferation[111] is supported by data showing correlation of testis volume with levels of inhibin B during infancy.[112] In an autopsy series, testes from 1-month-old boys showed greater volume and reduced levels of apoptosis in all cell types than in older boys.[113] In contrast, cohort[114] and longitudinal[110] analyses of living subjects using ultrasound suggest that the peak in neonatal testis size occurs at 5 months of age.

Puberty

Prior to puberty, mean testicular volume based on ultrasound/orchiometer estimations increases slowly from 0.5/1.6 mL at 1 year to 0.8/2.3 mL at 9 years of age.[115] During this period, Leydig cell hormonal activity remains quiescent, but Sertoli cells continue to produce AMH and inhibin B (Figure 68.6). A drop in AMH levels coinciding with an increase in inhibin B levels that may signal Sertoli cell maturation occurs at testis volumes of <2 mL and prior to a rise in serum testosterone, representing the earliest signs of puberty.[100,116] Other early markers of puberty include diurnal variations in urinary gonadotropin levels and an increase in early morning testosterone.[117] Clinically, an orchiometric volume of 3 or 4 mL is used to define the onset of puberty and occurs on average between 10.5 and 11.5 years of age.[117] Active production of spermatozoa occurs at a testicular volume of 6 mL.[117]

The high sensitivity to LH of the emerging adult Leydig cell population and consequent increases in intratesticular testosterone contribute to the rapid increase in germ cell proliferation, tubular diameter, and marked increase in testicular size.[111] With puberty, germ cells now replace Sertoli cells as the main testicular component (Figure 68.8). Complete spermatogenesis requires adequate levels of intratesticular (as opposed to serum) testosterone and multiple sex chromosomal and autosomal genes.[118] INSL3 levels best reflect the LH-stimulated differentiation status of Leydig cells and correlate well with early pubertal increases in LH and FSH.[119] Testosterone levels rise slightly later and reflect the acute Leydig cell response to LH (see above). INSL3 continues to rise after puberty and then falls in aging men, reflecting its usefulness as a marker of Leydig cell status.[119]

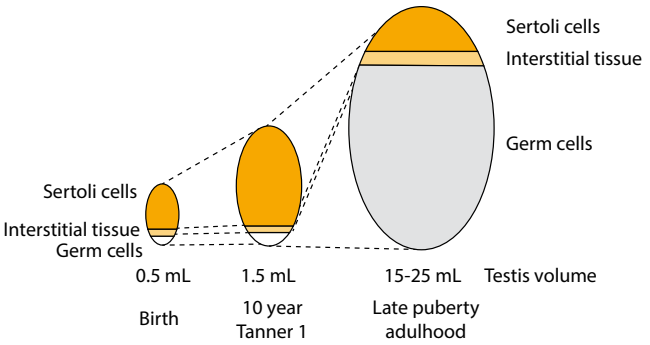

FIGURE 68.8 Schematic ontogeny of the evolution of testicular volume from birth to adulthood. Seminiferous tubules (Sertoli + germ cells) are always the major components of the testis. From birth and during the whole prepubertal period (i.e., until ages 9–14 years, Tanner stage 1), seminiferous tubule volume depends mainly on Sertoli cells, whereas the significant increase in testicular volume during pubertal development (i.e., between Tanner stages 1 and 5) is mainly due to germ cell proliferation. (From Grinspon RP et al. *J Pediatr Endocrinol Metab* 2012;25(1–2):3–11.)

Markers of Testicular Function in Hypogonadism

Activation of the HPG axis provides an opportunity to assess testicular function in neonates with abnormal genital development without the need for stimulation tests. After this period, serum gonadotropin levels fall and secondary increases are not always seen in boys with primary hypogonadism (defined broadly as any reduction in hormonal or spermatogenic function[118]) until puberty. The Sertoli cell markers AMH and inhibin B can be useful in evaluating hypogonadism in childhood as levels remain relatively high and do not require stimulation tests.[120] For example, in boys with hypogonadotropic hypogonadism, AMH and inhibin B levels may be lower than expected in childhood, but at the time of expected puberty, AMH levels are higher than normal for age due to lack of inhibition by testosterone. Inhibin B measurement may be a good first-line diagnostic test for delayed puberty, as very low levels are highly predictive of hypogonadotropic hypogonadism and less likely to reflect constitutional delay of puberty.[121] INSL3 may also be a good marker for pubertal onset,[122] and because it is not directly regulated by LH, levels may be normal in conditions associated with normally differentiated Leydig cells but abnormal steroidogenesis.[123]

In boys with anorchia, gonadotropin levels are abnormally high in infancy and decrease during childhood, but FSH is more likely to remain elevated than is LH, particularly prior to age 3.[124] In contrast, elevated levels of FSH and particularly LH in prepubertal boys with abdominal testes are possible but less common. AMH and inhibin B are also unmeasurable in anorchia but may also be very low or unmeasurable in boys with nonpalpable or abnormal testes, so that discrimination between these diagnoses based solely on hormone levels is not always possible.[124,125] However, when levels of AMH and/or inhibin B are low and FSH is high, hCG stimulation testing may not add additional useful information.[126,127]

Other Regulators of Testicular Function

New data suggest a reciprocal interaction between bone and testis extending beyond the known role of sex steroids on bone remodeling. Osteocalcin, a product of osteoblasts, regulates Leydig cell steroidogenesis by a novel mechanism that involves binding to Gprc6a, a G-protein-coupled receptor expressed in Leydig cells.[128] Interestingly, elevated LH levels do not compensate for reduced testosterone levels in osteocalcin knockout mice.

Hormones in the somatotropic axis also influence the reproductive axis at all levels, linking sexual maturation with physical growth and the availability of energy stores.[129,130] Growth hormone (GH) and IGF1, a mediator of GH signaling, positively impact the release of gonadotropin-releasing hormone from the hypothalamus and gonadotropins from the pituitary. GH and circulating and/or locally produced IGF1 also enhance expression of gonadotropin receptors and steroidogenesis in the testis.[129] The GH secretogogue ghrelin, a hormone activated in response to decreased energy stores, inhibits the HPG axis at the level of the hypothalamus and testis.[131] Ghrelin is expressed in Leydig and Sertoli cells, is a marker of Leydig cell differentiation, and in animal studies, inhibits steroidogenesis and expression of the pro-spermatogenic SCF (kit ligand).[39] Leptin, a hormone activated in response to satiety and complementary to ghrelin in energy homeostasis, has mixed effects in HPG axis regulation that include stimulation of LHRH release and inhibition of steroidogenesis.[132] Balanced ghrelin–leptin signaling is also important for the HPG axis, since unopposed ghrelin signaling appears to be responsible for the reduced steroidogenesis and germ cell apoptosis that occurs in mice with leptin deficiency.[133]

BLOOD–TESTIS BARRIER AND GERM CELL INJURY

With puberty and entry of the testis into meiosis, the BTB develops in order to support and maintain developing sperm in a sequestered environment.[134] The main components of the BTB are the basolateral membrane, apical membrane, and a tight junction complex between Sertoli cells (Figure 68.9) that provide anatomic and

FIGURE 68.9 Components of the BTB. Anatomical barrier: The basal membrane (BM), apical membrane (AM), and tight junction (TJ) form the Sertoli cell barrier. Substances within the circulation enter the interstitial space, but most of them (dots) are prevented from entering the adluminal compartment (thin line) of the testis by the anatomical component of the BTB. Physiological barrier: At the adluminal (thin line) and basal (thick line) membranes are the sites of specific transporters that control the movement of molecules (dots and stars) between the compartments, creating unique microenvironments for germ cell development and maturation in the testis. S, Sertoli cell; GC, germ cell, L, Leydig cell; B, blood vessel. (From Mital P et al. *Biol Reprod* 2011;84(5):851–8.)

physiologic barriers. The latter is determined by active transport across the basolateral and apical membranes. Proteins important for assembly of the BTB include testosterone, cytokines, TGFβs, RA, and junctional and cytoskeletal proteins.[135–137] Complex restructuring consisting of temporary disruption followed by reassembly is required for transport of preleptotene spermatocytes across the BTB at the appropriate stage of the spermatogenic cycle.[135]

The testis is an immunologically privileged site because normal fertility requires protection of spermatogenic cells from the host immune response. Immune privilege exists because multiple testicular cell types express regulatory factors that actively suppress this immune response and is not due to existence of the BTB per se.[138] However, the BTB limits passage of germ cell antigens from the tubule to immune cells in the interstitium (including macrophages, dendritic cells, and T cells) and transfer of antibodies into the tubule.[139] Failure of normal immunosuppression can occur as a result of trauma, infection, or other pathology and lead to testicular autoimmunity characterized by activation of immune cells, production of cytokines, germ cell apoptosis, and infertility.

Oxidative stress is a common testicular response to many types of injury or disease, including developmental disorders, genetic abnormalities, and environmental toxicants, and leads to excess germ cell apoptosis.[140] Oxidative stress occurs whenever there is an imbalance of production and removal of reactive oxygen species (ROS). For example, ischemia–reperfusion injury associated with testicular torsion initiates expression of inflammatory mediators, such as TNF-α and interleukin 1β (IL-1β). These activate mitogen-activated protein kinase (MAPK) pathways, neutrophil recruitment, and ROS production with resultant germ cell apoptosis.[141] Other sources of oxidative stress include heat stress related to varicocele and untreated cryptorchidism; exposure to toxicants such as phthalates, BPA, pesticides, and industrial chemicals; ionizing irradiation, chemotherapy; and genetic abnormalities.[140,142] The apoptosis pathways triggered by oxidative stress vary based on the source of injury but include the intrinsic pathway, mediated by members of the Bcl-2 (B-cell lymphoma 2) family of apoptotic regulators in mitochondria, and the extrinsic pathway, mediated by the cell death surface receptor Fas, expressed by germ cells and Fas ligand, secreted by Sertoli cells.[140,142] Heat and oxidative stress also cause DNA damage, which alters chromatin integrity and the potential for altered fertility and pregnancy outcomes.[143,144]

MAPK signaling, a common response pathway for potentially harmful cellular stimuli, is a key participant in the pathologic effects of oxidative stress that include apoptosis and the disruptive effects of toxicants on the BTB.[145] However, the MAPK pathway also responds to hormonal signaling by FSH and testosterone during spermatogenesis.[142] Normally, these hormones and physiologic levels of estrogen promote germ cell survival, while pharmacologic levels of androgen or estrogen can induce germ cell apoptosis.[142] These observations illustrate the dynamic balance between cellular proliferation and apoptosis required for healthy spermatogenesis, and therefore its susceptibility to disruption by diverse stimuli.

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CHAPTER
69

Gonads, Genital Ducts, and Genitalia

Steven E. Lerman, Irene M. McAleer, Alan L. Kaplan, and George W. Kaplan

Sex determination is the phenotypic expression of genotypic sex as defined by the presence or absence of a Y chromosome. The SRY gene, the testis-determining factor located on the Y chromosome, is responsible for male gonadal sex determination and subsequent male external and internal genitalia, testicular descent, regression of Müllerian ducts, and male gender identity. The absence of SRY expression results in female external and internal genitalia and a regression of the Wolffian ducts.[1]

Formation of the gonads begins during the first 3 weeks.[2–4] Approximately 30–50 germ cells become recognizable among the endodermal cells of the caudal portion of the yolk sac near the allantoic stalk. These begin to migrate by ameboid motion toward the genital ridge.

The hindgut begins to develop during this same time frame. Its development was described in Chapter 49. To briefly recapitulate, the hindgut, which is endoderm, sends a blind extension caudally, which meets the ectoderm of the body wall at the cloacal membrane. The cloacal membrane initially extends from the tail bud to the body stalk, but as the mesoderm grows, the extent of the cloacal membrane becomes smaller.

The gonads continue to develop during the fourth week but remain in an indifferent stage. At this time, it is impossible to determine the sex of an embryo by examination. The ventromedial surface of the urogenital ridge begins to thicken and bulge into the coelom as a separate genital ridge, which lies medial and parallel to the mesonephric ridge.

The germ cells, which have been migrating dorsally in the wall of the yolk sac and gut, reach the gonadal ridge by the middle of the fifth week (Figure 69.1). It is during this time that the genital tubercle appears on the ventral midline between the umbilical cord and the tail bud. The tubercle has a thin urogenital groove caudally, the floor of which is the cloacal membrane, and the sides are the urogenital folds. At this same time, the cloaca is divided into an anterior urogenital sinus and a posterior rectum by the urorectal septum.

During the sixth week, an indifferent gonad is recognizable in both sexes and consists of superficial germinal epithelium and an internal blastema derived from ingrowth of coelomic epithelium. The blastema forms into primary or medullary sex cords, and the germ cells and mesenchyme come to lie between these cords. The urogenital ridge is attached broadly near the root of the mesentery. In both sexes, a groove appears in the urogenital ridge located laterally on the mesonephros near the cephalic end. The cranial end of this groove remains open, while caudally it begins to close into a tube (the Müllerian duct) (Figure 69.2). There is progressive caudal growth of the solid, blind end of the Müllerian duct, guided by the mesonephros. Near the cloaca, the urogenital ridges swing mesiad into the genital cord. The cranial end of the Müllerian duct is forced laterally by the enlarging suprarenal glands and kidneys. Hence, each Müllerian duct has two bends, a cranial one and a caudal one (Figure 69.3).

During the seventh week in the male, the attachment of the gonads to the mesonephros becomes the mesorchium. The medullary sex cords fuse with mesonephric tubules to form ductuli efferentes (Figure 69.4). Some mesonephric tubules cephalad to this area persist as vestigial structures associated with the epididymis and spermatic cord (the appendix epididymis, the superior and inferior vasa aberrantia, and the paradidymis). The sex cords become separated from the surface epithelium of the gonad by small cells that eventually form the tunica albuginea. The primordial germ cells become incorporated into the testis cords, and these cords become arranged radially, separated by a proliferation of mesenchyme. The cords eventually converge toward the blastemal mass, emerging as the primordia of the rete testis. In the female, at this time the round ligament begins to form. There are known teratogens that disrupt normal embryogenesis resulting in abnormalities of the genitalia (Table 69.1).

The genital tubercle elongates into a phallus, and its tip rounds into the glans (Figure 69.5). The Sonic hedgehog (SHH) signaling pathway, important in genitourinary tract development, has been shown to be indispensible for the establishment of male external genitalia, and likely facilitates the masculinization process.[5] Genital swellings appear lateral to the phallic base. The urogenital sinus opens at the base of the phallus by rupture of the cloacal membrane. In the male, the corpora cavernosa begin to appear from mesenchymal columns in this area (Table 69.1).

The upper five-sixths of the mesonephric ridge is lost by the eighth week and becomes the diaphragmatic ligament of the mesonephros, which eventually will become the suspensory ligament of the gonad.

In the male, the tunica albuginea has formed a definite encapsulating layer on the gonad, and the gubernaculum begins to form. The phallus elongates, as does the urethral groove, and the genital swellings rotate caudad.

In the female, clusters of indifferent cells and primordial germ cells appear. These fall into a dense primary cortex and a looser primary medulla. A mass bulges from the medulla into the mesovarium to form the rete ovarii (Figure 69.6). The suspensory ligament of the ovary is formed from the cephalic end of the genital ridge, while the proper ligament of the ovary is formed from the terminal part of the genital

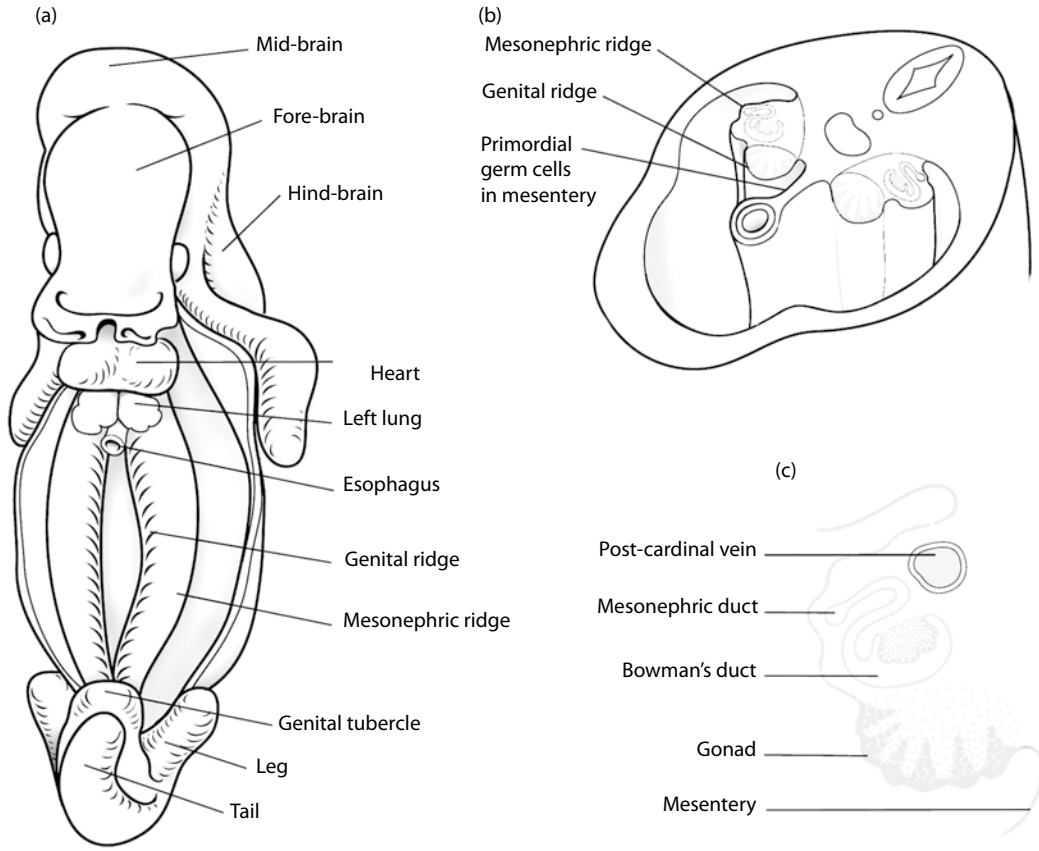

FIGURE 69.1 Urogenital ridge in the human: (a) 9 mm ventral view; (b) 7 mm transverse view; and (c) 10 mm transverse view. (Reproduced from Arey LB. *Developmental Anatomy*, 6th edn. Philadelphia: WB Saunders, 1974. With permission.)

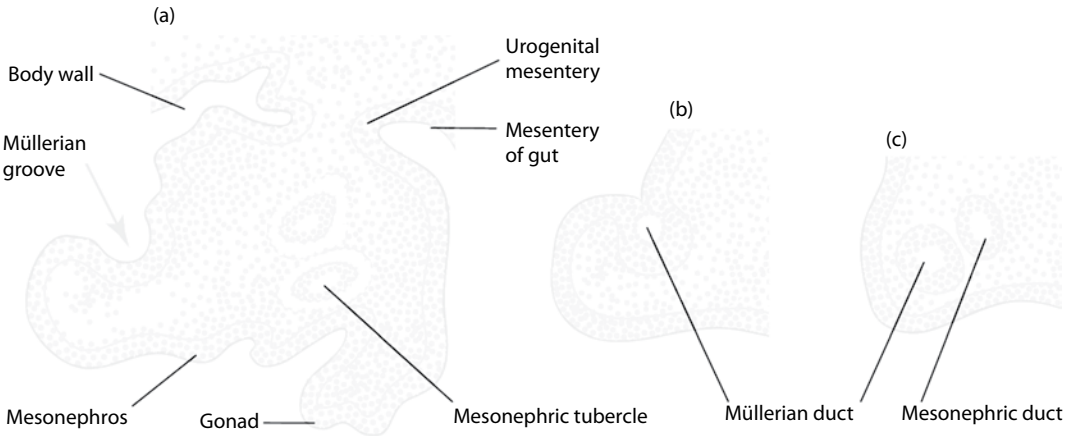

FIGURE 69.2 Origin of the human Müllerian duct at the 12 mm stage: (a) through the open groove; (b) slightly lower level, showing closure; and (c) still lower, showing a tube. (Reproduced from Arey LB. *Developmental Anatomy*, 6th edn. Philadelphia: WB Saunders, 1974. With permission.)

ridge and unites the caudal end of the ovary to the transverse bend of the Müllerian duct and eventually to the uterus.

The mesonephros consists of 34 pairs of tubules by the ninth week, but half of them are nonfunctional. This is the end of the stage of maximal mesonephric development. The cranial 8–15 pairs project against the rete testis or rete ovarii. The caudal ends of the Müllerian ducts have now fused medially and end blindly at Müller's tubercle. The mesonephric ducts are now lateral to the Müllerian duct caudally.

Cowper's gland in the male and Bartholin's gland in the female, which are homologs, arise as a pair of solid buds from the endodermal epithelium of the urogenital sinus distal to Müller's tubercle. In the male, they extend backwards, paralleling the urogenital sinus, and penetrate the mesenchyme of the corpus cavernosum urethrae and become glandular. They open into the bulbus urethrae. In the female, they open into the vestibule near the hymen.

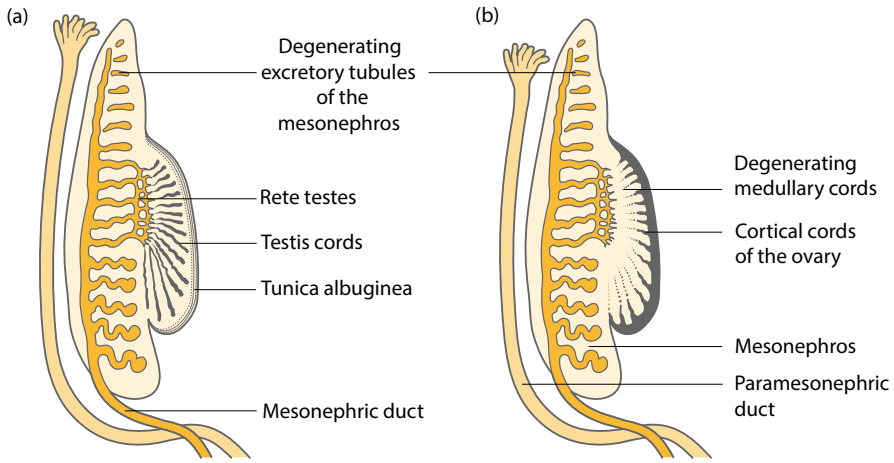

FIGURE 69.3 Diagram of the genital ducts in the 6th week of development in the male (a) and female (b). The mesonephric and Müllerian ducts are present in both. Note the excretory tubules of the mesonephros and their relationship to the developing gonad in both sexes. (Reproduced from Sadler TW. *Longman's Medical Embryology*, 7th edn. Philadelphia: Williams & Wilkins, 1995. With permission.)

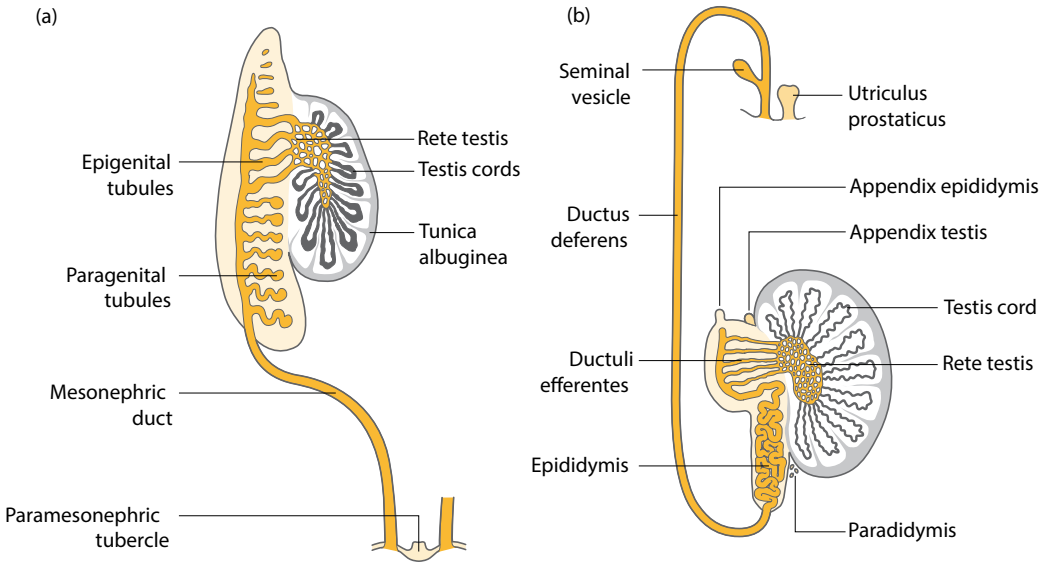

FIGURE 69.4 (a) Diagram of the genital ducts in the male in the 4th month of development. Cranial and caudal (paragenital tubule) segments of the mesonephric system regress. (b) Diagram of the genital ducts after descent of the testis. Note the horseshoe-shaped testis cords, rete testis, and efferent ductules entering the ductus deferens. The paradidymis is formed by remnants of the paragenital mesonephric tubules. The müllerian duct has degenerated except for the appendix testis. The prostatic utricle is an outpocketing from the urethra. (Reproduced from Sadler TW. *Longman's Medical Embryology*, 7th edn. Philadelphia: Williams & Wilkins, 1995. With permission.)

By the 10th week, all the mesonephric tubules have become discontinuous. The gonads in both sexes lie at the boundary of the pelvis and the abdomen. In the male, the external genitalia are becoming visible as male structures as a result of secretion of testosterone by the fetal testis. The phallus has become the penis. The edges of the urethral folds begin to fuse progressively from posterior to anterior, forming the urethra and the median raphe. The genital swellings become scrotal swellings, which fuse, forming a scrotal septum and raphe.

In the 11th week, the prostate arises as multiple outgrowths of endoderm both above and below the mesonephric ducts. These outgrowths arise in five different groups, each of which corresponds to a future prostatic lobe. The buds grow into the surrounding mesenchyme, which in turn provides both connective tissue and smooth muscle. In the female, the homologs of the prostate are the urethral glands, which are drained by Skene's ducts on each side.

Littre's glands bud from the male urethra in the 12th week. In the female, homologs of Littre's glands bud into the vestibule. In the male, the processus vaginalis appears as an outpouching at the internal inguinal ring, and the testis lies nearby. The gubernaculum has already formed. The Müllerian ducts degenerate owing to the secretion, by Sertoli cells, of Müllerian inhibiting factor (MIF). Müllerian remants in the male are the appendix testis

TABLE 69.1 Genitourinary (GU) tract teratogens

Teratogen	Potential GU defect
Maternal hyperthermia	Micropenis
Rubella virus (congenital rubella)	Hypospadias, cryptorchidism
Progestational agents	Ambiguous genitalia
Oral contraceptives	Hypospadias
ACE inhibitors	Renal dysplasia
Ethanol (fetal alcohol syndrome)	Hypospadias, hydronephrosis
Anticonvulsants	Hypospadias, ambiguous genitalia, cryptorchidism
Cocaine	Eagle–Barrett syndrome, hypospadias, hydronephrosis
Vitamin A (excessive)	Hydronephrosis, hypospadias

Abbreviation: ACE, angiotensin-converting enzyme.

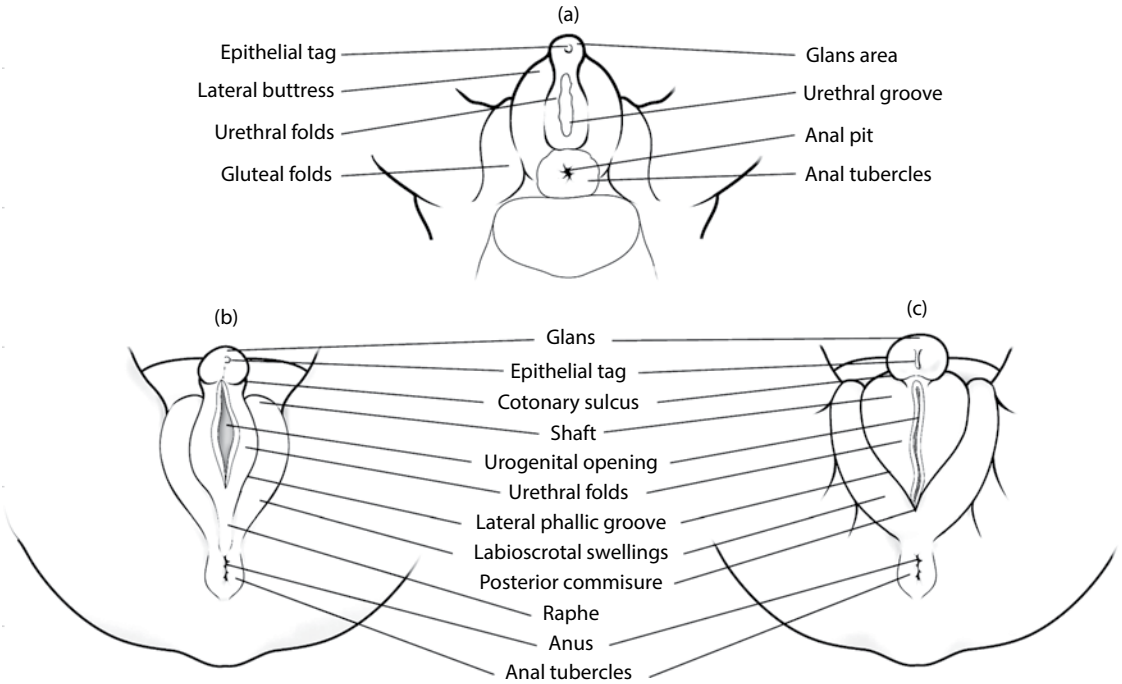

FIGURE 69.5 Developing external genitalia of the human: (a) 7th week; (b) male, 10th week; and (c) female, 11th week. (Reproduced from Gray SW, Skandalakis JE. *Embryology for Surgeons*. Philadelphia: WB Saunders, 1972, 496. With permission.)

from the cranial end and the prostatic utricle from the caudal end of the Müllerian duct (Table 69.2).

In the female, the secondary ovarian cortex begins to form in the 12th week by division of cells of the ovarian blastema and by new growth of germinal epithelium. The early ova regress and form the medulla. The ovaries at this time lie at the pelvic brim. The round ligament is complete. Vaginal and uterine musculature appears from the mesenchyme surrounding the Müllerian ducts. The distal portions of the Müllerian ducts have fused below the caudal bend (Figure 69.7).

In the 13th week, in the male, the seminal vesicles develop as lateral branches off the mesonephric duct. Branching of these seminal vesicles is evident by the fourth month of fetal life, and eventually a muscular coat is gained from the mesenchyme. In the female, the mesonephric ducts begin to regress. Elongation of the fetal pelvis causes a solid epithelial cord to form between the end of the Müllerian ducts and the urogenital sinus; this cord will become the upper vagina.

During the 14th week, the penile shaft continues to elongate in the male, and the urethra has fused to the base of the glans penis. The penile shaft has a ventral deflection.[6] The prepuce now begins to form as a fold of skin that grows distally. By 5 months of gestational age, preputial formation is complete. The prepuce then fuses to the glans and reseparates from it under the influence of testosterone by the formation of small clefts in the preputial sac. This procedure of separation is incomplete at birth and continues for several years thereafter.

By the 16th week, maximal degeneration of the mesonephric tubules has been attained. The muscles of the perineal floor are visible. The epithelium of Cowper's and Bartholin's glands is glandular in nature. In the

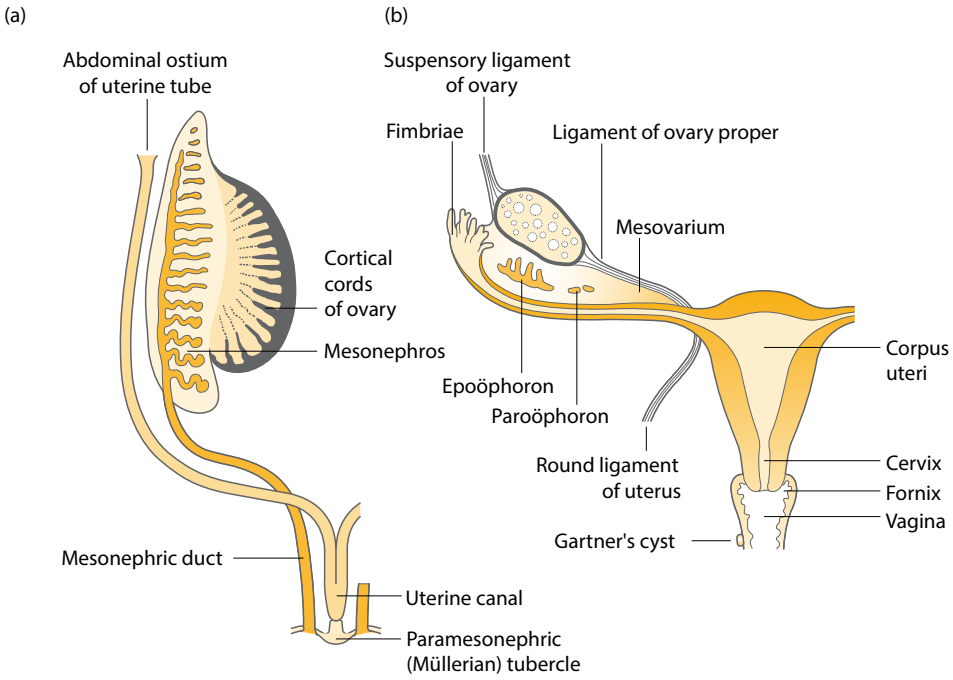

FIGURE 69.6 (a) Drawing of the genital ducts in the female at the end of the 2nd month of development. Note the müllerian tubercle and formation of the uterine canal. (b) Drawing of the genital ducts after descent of the ovary. The only parts remaining from the mesonephric system are the epoöphoron, paroöphoron, and Gartner's duct. Note the suspensory ligament of the ovary, ligament of the ovary proper, and round ligament of the uterus. (Reproduced from Sadler TW. *Longman's Medical Embryology*, 7th edn. Philadelphia: Williams & Wilkins, 1995. With permission.)

TABLE 69.2 Embryologic remnants

Male	Müllerian remnants	Appendix testis
		Prostatic utricle
Female	Wolffian remnants	Epoophoron
		Paraoophoron
		Gartner's duct

testis, interstitial cells are very abundant. In the female, the vagina begins to form a lumen, as the fornices appear as clefts in the solid epithelial cord distal to the fused Müllerian ducts. The uterus forms as a fusion of Müllerian ducts as they move ventrally and medially. Inappropriate fusion can result in uterine structural abnormalities, such as bicornuate uterus (Figure 69.8). During this fusion, the broad ligaments are formed. The cervix and the fallopian tubes are now evident.

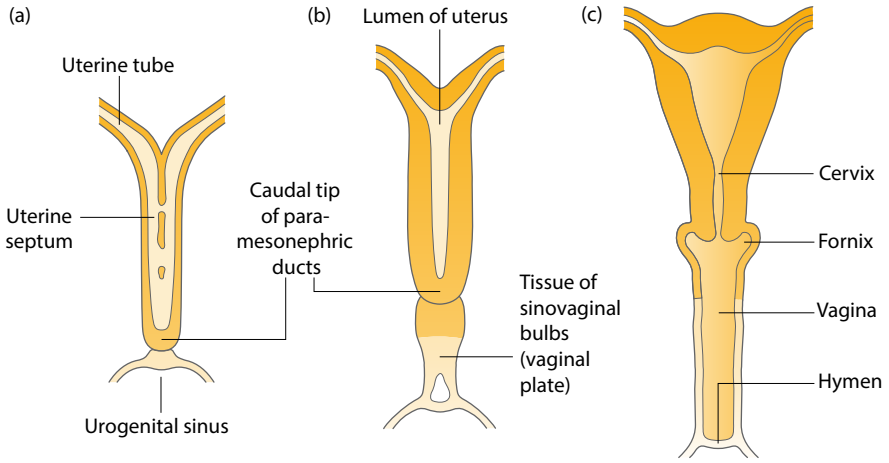

FIGURE 69.7 Schematic drawing showing formation of the uterus and vagina: (a) at 9 weeks, note the disappearance of the uterine septum; (b) at the end of the 3rd month, note the tissue of the sinovaginal bulbs; and (c) in the newborn, the fornices and the upper portion of the vagina are formed by vacuolization of the Müllerian tissue and the lower portion of the vagina is formed by vacuolization of the sinovaginal bulbs. (Reproduced from Sadler TW. *Longman's Medical Embryology*, 7th edn. Philadelphia: Williams & Wilkins, 1995. With permission.)

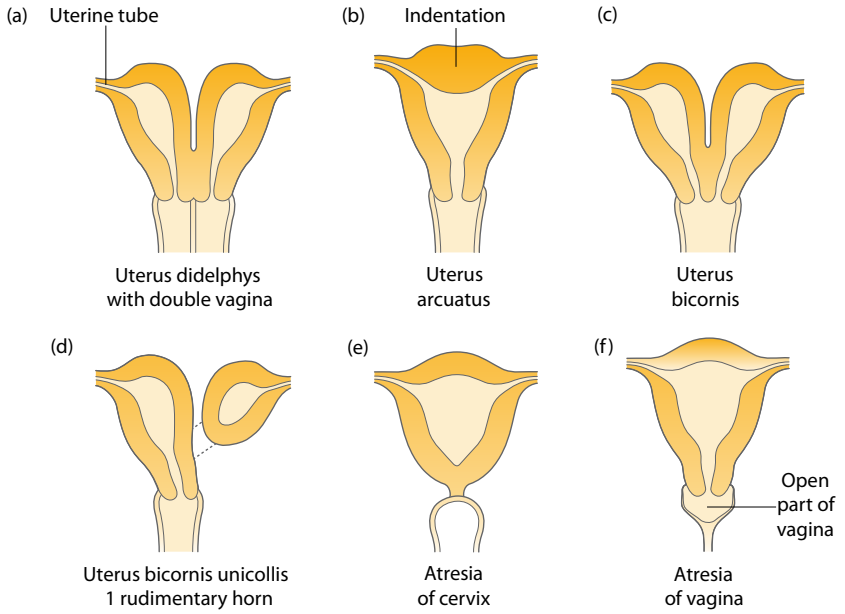

FIGURE 69.8 Schematic representation of the main abnormalities of the uterus and vagina, caused by persistence of the uterine septum or obliteration of the lumen of the uterine canal. (Reproduced from Sadler TW. *Longman's Medical Embryology*, 7th edn. Philadelphia: Williams & Wilkins, 1995. With permission.)

The vaginal lumen and the prepuce are completely formed by the 20th week. The penile shaft is now straight.[6] Homologous structures between males and females and their embryologic origin are listed in Table 69.3.

The tunica albuginea of the ovary forms during the 24th week. In the male, the lumens of the rete tubules and cranial mesonephric tubules become continuous and form the efferent ductules of the epididymis. The cranial end of the mesonephric duct convolutes, forming the body of the epididymis. The caudal end remains straight, forming the ductus deferens. The terminal end of the mesonephric duct forms the ejaculatory duct. The ampulla of the vas deferens forms from dilation of the ejaculatory duct. The processus vaginalis in the male now begins to move through the inguinal canal.

Formation of the seminal vesicles in the male is complete by the 28th week. The processus vaginalis has herniated through the abdominal wall, formed the inguinal canal, and reached the scrotum. The testis then begins to descend toward the scrotum. Several factors are hypothesized to influence testicular descent. These include gubernacular guidance, increased intra-abdominal pressure,[7] and possibly the release of a substance, descendin, from the normal testis.[8] In addition, the genitofemoral nerve has been studied as a potential factor in inducing testicular descent.[9] With normal factors intact, the testicle will reach the ipsilateral scrotum during the third trimester. Testis descent occurs in 60% of males by 30 weeks and 93% of males by 32 weeks.[10] Cryptorchidism is a frequent anomaly whose etiology has been extensively studied but is still incompletely understood. Some instances appear to be due to intrauterine endocrine failures, whereas others seem mechanical. Intra-abdominal testes might result if the processus vaginalis did not form.

TABLE 69.3 Embryologic homologs

Embryologic structure	Male	Female
Urogenital sinus	Prostatic urethra, prostate	Urethra, upper vagina
Genital tubercle	Glans penis	Clitoris
Genital folds	Urethra, penile shaft	Labia minora
Genital swellings	Scrotum	Labia majora
Mesonephric duct	Appendix epididymis	Appendix vesiculosa
	Duct of epididymis	Duct of epoophoron
	Ductus deferens	Gartner's duct
	Ureter, pelvis, collecting tubules	Ureter, pelvis, collecting tubules
	Ejaculatory duct, seminal vesicles	
Paramesonephric duct	Appendix testis	Hydatid of Morgagni
		Uterus, fallopian tubes

Ectopic testes might result if the path of descent were obstructed or if the gubernaculum went astray, failing to define a path for the testis to follow into the ipsilateral scrotum. The descent of the ovary is quite comparable to that of the testicle, but the gubernaculum fuses with the lateral margin of the uterus, which therefore arrests descent of the ovary in the pelvis. Failure of fusion of the gubernaculum to the uterus may allow the ovary to descend into the labia majora.

Major anomalies of these genital organs are frequent, including intersex, hypospadias, and cryptorchidism. If the testis-determining factor is present, a testis will develop. In the presence of the testis, the MIF will be released by Sertoli cells and lead to regression of the Müllerian ducts. In addition, elaboration of testosterone from Leydig cells will cause development of the mesonephric ducts and masculinization of the internal ducts. Masculinization of the external genitalia is dependent on the conversion of testosterone to 5-dihydrotestosterone. Failure of this conversion helps to explain some cases of ambiguous genitalia. In the absence of a testis, an ovary (or streak gonad) forms, the Müllerian structures persist, and the external genitalia are feminine.

Hypospadias represents arrested formation of the phallus and phallic urethra. In many instances, the distal hypospadiac urethra is dysplastic, as is the surrounding corpus spongiosum.[11] With severe forms of hypospadias, a small Müllerian remnant may persist as a diverticulum off the prostatic utricle.

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CHAPTER 70

Disorders of Sex Development

Joao Luiz Pippi Salle and Rodrigo L. P. Romao

INTRODUCTION

The term *disorders of sex development* (DSDs) is a relatively recent addition to pediatric urology practice. It was forged in 2006 as part of a consensus statement elaborated on following a multidisciplinary meeting involving endocrinologists, urologists and pediatric surgeons, geneticists, psychologists, and representatives from advocacy groups.[1,2] The consensus postulated that any expression that could give rise to an idea of an intersex state, hermaphroditism or "third gender" should be abandoned. Classical terms such as *male and female pseudohermaphroditism* were thus banished (Table 70.1). DSD was purposely picked as a broad term defined as a congenital condition where the development of chromosomic, gonadal, or anatomical sex is atypical.[2,3] Hence, it widens the scope of the previous terminology (*intersex*), which included only conditions associated with some sort of genital ambiguity, and incorporates, for example, patients with abnormalities in the sexual chromosomes (such as Turner or Klinefelter syndromes) or others with discordance between genetic and phenotypic sex (e.g., complete androgen insensitivity syndrome [CAIS]). For that reason, establishing the true incidence of DSDs is impossible.

Despite some criticism on the suitability of the term *disorders*, with some suggesting that a nonpathological nomenclature should be sought, such as "atypical sex anatomy,"[4] the consensus statement has been well accepted by the medical and patient community worldwide;[5–8] the vast majority of publications related to this subject after 2006 have adhered to the classification and nomenclature proposed therein. Therefore, it is used throughout this chapter.

The first section of this chapter is a detailed description of the normal development of the external and internal genitalia, outlining the most recent discoveries in terms of genetic mechanisms associated with it. Second, the approach to the newborn or young infant with genital ambiguity is presented, following a detailed explanation of the DSD classification. Finally, each diagnosis is presented separately, along with specific medical and surgical management.

GENITAL DEVELOPMENT

Primordial germ cells are initially seen at the outer ectodermal layer of the embryo and undergo migration until they settle in the urogenital ridge, which is the site of development of the future gonad, kidney, and adrenal gland. The cornerstone of sex determination in humans is gonadal function.[9] The gonads regulate all changes that will eventually lead to the definition of the phenotypic sex. The gonads are undifferentiated initially and develop into a testicle or ovary around the sixth week of embryogenesis. In DSD patients, two other types of gonads can be seen: streak gonads, consisting of ovarian stroma without follicles, or germ cells and ovotestis, comprising a mixture of normal ovarian and testicular tissues.

In the past, it was widely accepted that internal and external female development were the "default" pathway, which would only be altered by the presence of a testicle. That concept was largely based on Jost et al.'s experiments with castrated rabbits.[10] Recent discoveries regarding the genetic basis of sexual development and differentiation have cast shadow on this theory and suggested that both male and female phenotypes are induced individually by a specific genetic makeup. Currently, the gene known as SRY (sex-determining region mapped to the short arm of the Y chromosome) is regarded as the male-defining factor in humans; however, the presence of this gene does not seem to be sufficient for testis induction; i.e., SRY is not the immediate inducer of testis formation. Rather, it appears to upregulate an ultimate testis-inducing gene (mechanism not totally elucidated, possible role for R-spondin 1) called SOX9, mapped to chromosome 17, which in turn upregulates PGD2 and FGF9. Both genes maintain SOX9 expression through a positive feedback loop, establishing the male pathway.[11]

Despite also playing a role in testicular development, DAX1 has been implicated as a likely X-linked female-determining gene.[12] WNT4 could be the female counterpart of SOX9, since it has also been implicated in suppression of both male sexual differentiation and gonadal androgen production in females.[13] Overexpression of either DAX1 or WNT4 antagonizes testis formation. In XX gonads, WNT4 induces beta-catenin, which results in silencing of FGF9 and SOX9.[11] The WNT4 signaling pathway plays a role in ovarian development and maintenance, whereas FOXL2 is involved in granulosa cell differentiation and follicle development,[11] thus acting as an ovarian-inducing gene as well.[12] Finally, RSPO1 is also a suppressor of the SOX9 gene.[11]

Internal Genitalia

Once the gonad differentiates into a testicle, two hormones drive differentiation of the internal genitalia: testosterone and anti-Mullerian hormone (AMH). The former is

TABLE 70.1 Comparison of current nomenclature with previous ones

Previous	Proposed by 2006 consensus
Intersex	Disorder of sex development (DSD)
Male pseudohermaphroditism	46 XY DSD
Female pseudohermaphroditism	46 XX DSD
XX male	46 XX testicular DSD
True hermaphroditism	Ovotesticular DSD
Any situation with chromosome mosaicism	Sex chromosome DSD

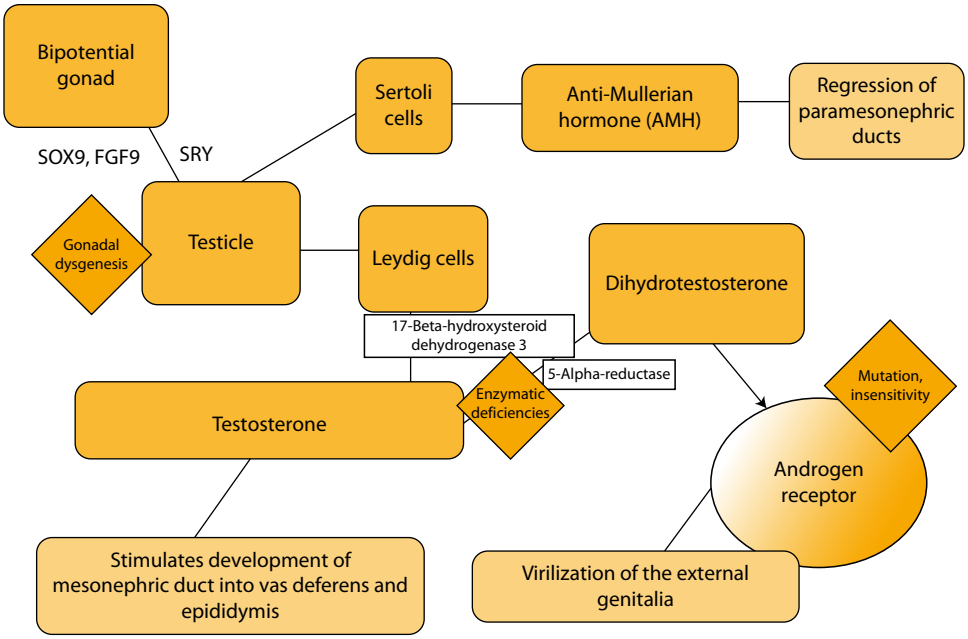

FIGURE 70.1 Schematic representation of steps modulating internal and external male genitalia differentiation. The diamond-shaped boxes depict potential areas for disruption, leading to DSDs.

produced by Leydig cells and binds to the nuclear androgen receptor (AR) of the fetus, thus stimulating the development of the Wolffian (mesonephric) ducts into male structures, such as the vas and epididymis; the latter is synthesized by Sertoli cells and causes regression of the Mullerian (paramesonephric) ducts, thereby inhibiting their differentiation into a uterus, fallopian tubes, cervix, and upper third of a vagina (Figure 70.1).

External Genitalia

Virilization of the external genitalia, characterized by fusion of labioscrotal folds forming the scrotum, urethral plate tubularization, and development of the genital tubercle into a penis, is the result of the action of dihydrotestosterone (DHT) on the AR present on genital skin. DHT is converted from testosterone (which in turn is synthesized by the Leydig cells from cholesterol) by 5-alpha-reductase type 2 (SRD5A2) and represents a much more potent androgen. Recently, it has been demonstrated that the fetal testis can also produce DHT directly through the so-called backdoor pathway;[14] the same authors have postulated that both the classic (from testosterone) and alternative pathways are essential for normal human male development. In the absence of DHT, the genital tubercle will become the clitoris and the labioscrotal folds will form the labia majora and minora. It should be noted that the development of a normal female phenotype is contingent on normal levels of estrogen produced by the ovaries (for example, patients with Turner's syndrome, who have bilateral streak gonads, depict an infantile external genitalia and lack of breast development), and therefore it should not be seen as the "basic" or default phenotype.[12]

Most DSD conditions will result from gonadal dysfunction (dysgenesis) or inadequate hormonal (androgen) action (either excessive or insufficient), which clinically will translate into either virilization of the female fetus or undermasculinization of the male one.

Studies using knockout mice, as well as research involving families affected by variable types of DSDs, have elucidated some genetic mechanisms associated with the development of gonadal dysfunction, as detailed below.

The urogenital ridge develops from the intermediate mesoderm. Some genes have been identified as critical in the formation of the urogenital ridge, which explains why they are associated not only with gonadal but also

TABLE 70.2 Genes and genetic syndromes known to be associated with DSDs

Disorder of sex development	Gene	Locus	Genetic syndrome/associated disorders
CAH	CYP21A2 (21-hydroxylase deficiency)	6q	n/a
	CYP11B1 (11-beta-hydroxylase deficiency)	8q	
	HSD3B2 (3-beta-hydroxysteroid dehydrogenase type 2)	1p	
CAIS or PAIS	AR	Xq	n/a
5-Alpha-reductase deficiency	SRD5A2	2p	n/a
17-Beta-hydroxysteroid dehydrogenase deficiency	HSD17B3	9q	n/a
Persistent Mullerian duct syndrome	AMH AMH receptor	19p 12q	n/a
Ovotesticular DSD, testicular DSD, and dysgenetic testicle	SRY	Yp	n/a
Dysgenetic testicle	WT1	11p13	WAGR, Denys–Drash, and Frasier syndromes
Dysgenetic testicle	ATRX	Xq	Alpha-talassemia and mental retardation
XY DSD (inborn error of cholesterol synthesis)	DHCR7	11q	Smith–Lemli–Opitz syndrome
Dysgenetic testicle	SOX9	17q	Camptomelic dysplasia

with renal or adrenal problems. Wilms' tumor suppressor gene (WT1) is crucial for gonadal and renal development. Frasier and Denys–Drash syndromes are caused by a WT1 mutation that will affect both the gonads and the kidneys, leading to DSDs. Steroidogenic factor 1 (SF1 encoded by NR5A1) and the "duplicated in adrenal hypoplasia congenital on the X chromosome (DAX1) proteins" are essential for gonadal and adrenal development.[9] Mutations in NR5A1 have been identified not only in patients with 46 XY gonadal dysgenesis, but also with isolated hypospadias and ovarian insufficiency.[15,16] Recently, another gene associated with intermediate mesoderm formation, GATA4, has been implicated in human testicular development, and a mutation was identified in a patient with 46 XY DSD and a congenital cardiac anomaly.[17] A recent genome-wide study in individuals with 46 XY gonadal dysgenesis identified copy number variations in many of the aforementioned genes, further supporting their role in the intricate process of gonadal development and differentiation.[18] Analysis of two families with cases of 46 XY DSD underlined a causative effect of mutations in MAP3K1.[19]

Molecular mechanisms of excessive or insufficient androgen action will be highlighted in the respective sections. Table 70.2 summarizes genes and genetic syndromes that have been demonstrated to be associated with DSDs.

CLASSIFICATION

The current DSD classification follows the patient's karyotype, and three main groups are recognized: 46XY DSD, 46XX DSD, and sex chromosome DSD (mosaic karyotype, most commonly 45X/46XY). Further identification of the source of the problem, i.e., gonad structure or function, androgen pathway and receptor, etc., will lead to a specific diagnosis.[1,2] Most common causes of DSDs divided by karyotype are depicted in Table 70.3.

Most patients with a DSD present in the neonatal period with genital ambiguity. Clinical scenarios that should trigger evaluation for DSDs are overt genital ambiguity, female external genitalia that appears virilized (i.e., enlarged clitoris, posterior labial fusion, and inguinal or labial mass), or male external genitalia that appears undervirilized (bilateral nonpalpable testicles, micropenis, association of hypospadias, and undescended testicles).

A significant proportion (10%–20%) of patients can present later in life (childhood or even young adulthood), and for those, the absence of ambiguity is the rule. Reasons for referral of female patients include palpable gonad within an inguinal hernia; absent, delayed, or incomplete puberty; virilization; and primary amenorrhea. In males, breast development, gross cyclic hematuria, and sometimes simply infertility flag the possibility of a DSD. In pediatric medicine, as karyotype has become more common, discordance between genital appearance and karyotype ordered for issues unrelated to gender assignment is another reason for referral to DSD clinics.[20,21]

APPROACH TO THE NEWBORN WITH GENITAL AMBIGUITY

Newborns with genital ambiguity should be evaluated on an urgent basis for two reasons: to rule out congenital adrenal hyperplasia (CAH), since the salt-wasting form of the disease can be life threatening, and to provide a male or female gender assignment after a thorough, timely investigation. The first challenge is to define which patients in fact have ambiguous genitalia, as opposed to minor genital abnormalities (e.g., mild clitoral enlargement or isolated

TABLE 70.3 Most common DSD diagnoses divided by karyotype

	XX DSD	XY DSD	Sex chromosome DSD
Disorders of gonadal development	• Ovotesticular DSD • XX sex reversal (testicular DSD) • Gonadal dysgenesis	• Pure gonadal dysgenesis • Partial gonadal dysgenesis • Ovotesticular DSD • Gonadal regression or vanishing testis syndrome	• 45 X/46 XY—Mixed gonadal dysgenesis or ovotesticular DSD • 47 XXY—Klinefelter syndrome • 45 X—Turner syndrome
Disorders related to androgen synthesis or action	**Androgen excess**	**Androgen action**	
	a) Maternal • Luteoma • Exogenous (medications)	Androgen insensitivity syndrome (complete or partial)	
	b) Fetoplacental • Aromatase deficiency	Androgen synthesis	
	c) Fetal • Congenital adrenal hyperplasia (21-hydroxylase deficiency most common)	• LH receptor mutation • 17-Beta-hydroxysteroid dehydrogenase deficiency • 5-Alpha-reductase deficiency • Male CAH (e.g., 3-beta deficiency)	

distal hypospadias), and therefore avoid overinvestigation. After identifying one of the scenarios listed in the section above, the first step is to request an evaluation by an expert in DSDs, who works as part of a multidisciplinary team. Even before the first assessment is initiated, some general principles should be kept in mind: one should refrain from making comments or statements based on the appearance of the external genitalia alone; a long-term care plan should be discussed in the setting of a multidisciplinary, holistic, patient-centered clinic using the best level of evidence available; family concerns should be addressed promptly, openly, and confidentially by professionals with the best communication skills, without withholding detailed information.[22]

Prenatal Diagnosis

The second-trimester ultrasound has an accuracy of 98% for determining the fetal sex. The presence of ambiguous genitalia is amenable to sonographic detection. Following such detection, a detailed scan seeking associated anomalies (renal are the most common) should be performed. Cell-free DNA (cfDNA) from the fetus is detectable in maternal blood 4–6 weeks after fecundation;[23] therefore, Y material could be identified offering insight into the possible diagnosis. In the presence of a Y chromosome, undervirilized genitalia (hypospadias, penoscrotal transposition, etc.—see below for details), and sonographic signs of placental insufficiency (such as intrauterine growth retardation), no additional tests are required, since this association has been well documented[24,25] and is known not to be coupled with added abnormalities.

In fetuses with abnormal genitalia, normal intrauterine growth, and no evidence of Y DNA, amniocentesis could be offered to confirm female gender with a karyotype and assess the steroid profile (see "Diagnostic Tests" section below), hence allowing an early diagnosis of an otherwise unsuspected CAH case. Prenatal treatment of CAH will be discussed in detail in the corresponding section.

In a series of 140 individuals followed by a multidisciplinary DSD clinic, 24% were identified prenatally, and the most common diagnoses were penoscrotal hypospadias associated with transposition of the scrotum and no specific genetic cause (17%) and CAH due to 21-hydroxylase deficiency (14%),[26] thus highlighting the limited but still valid role of prenatal diagnosis for genital ambiguity.

Discordance between the sonographic appearance of the genitalia and karyotype performed by amniocentesis for an unrelated reason is another contemporary source of DSD diagnosis. Hence, male-appearing external genitalia in XX patients and vice versa may trigger a suspicion for a DSD. Furthermore, the finding of a 45X/46 XY karyotype prenatally is not necessarily associated with genital ambiguity, since the phenotype in patients with such abnormality is highly variable,[27] and some publications have suggested that up to 90% of patients detected prenatally can be phenotypically normal.[28,29] Figure 70.2 depicts a suggested algorithm for the investigation of prenatally detected genital abnormalities.

History

A detailed history should focus on family history of DSDs, parental consanguinity, unexplained previous infant deaths, maternal ingestion of drugs (particularly progestagens and steroids), use of assisted reproductive technologies, and results of prenatal tests. A history of maternal virilization or severe acne during pregnancy is also valuable. During the first interview, care should be taken to ascertain the degree of knowledge parents might already have about their baby's condition and DSDs. A careful perinatal history focused on evidence of prematurity, intrauterine growth retardation, or other signs of placental insufficiency should also be obtained because of the aforementioned association of those conditions with undervirilization of the male genitalia.[24,25] As the parents may not know details of a family history of DSDs, it is important to ask about a history of hypospadias, amenorrhea, and infertility.

Physical Examination

Physical examination should initially focus on general findings and potentially life-threatening problems, like the

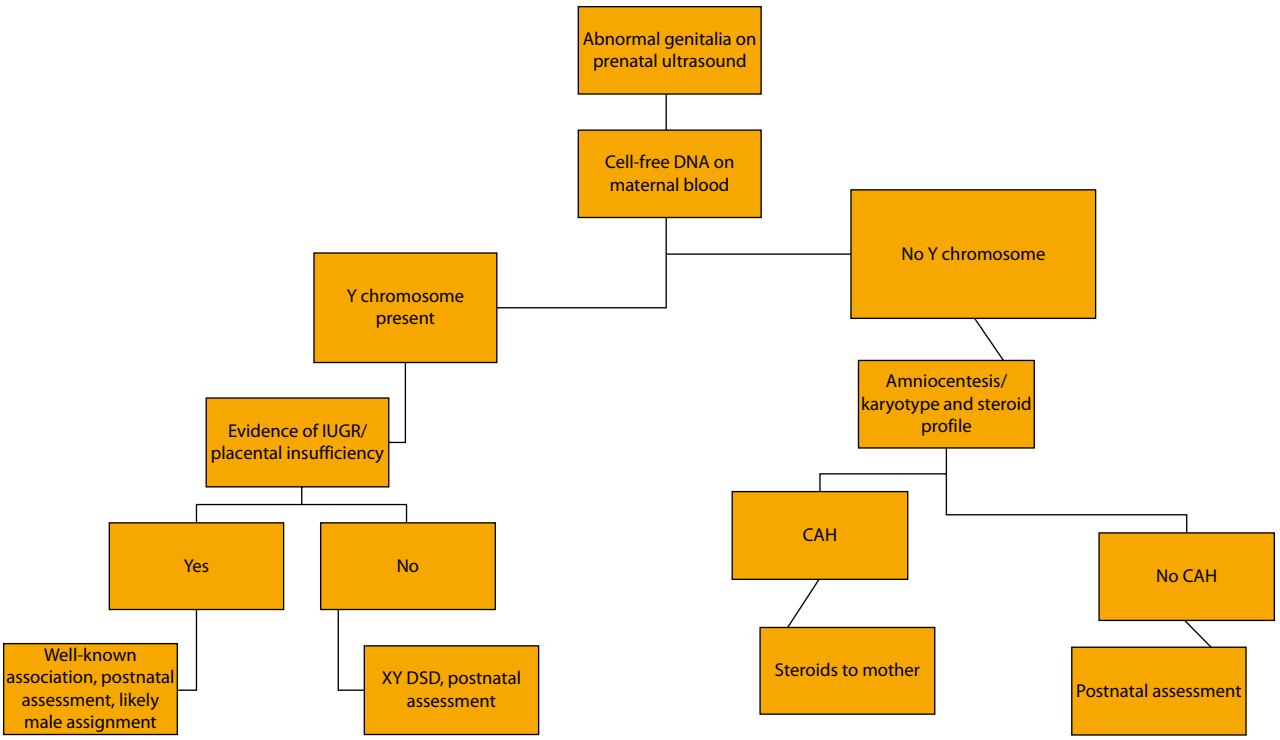

FIGURE 70.2 Suggested algorithm for the pre- and postnatal investigation of patients with genital abnormalities on ultrasound.

presence of severe dehydration that can be associated with salt-wasting CAH (which usually happens after 1–2 weeks of life), followed by inspection for signs of dysmorphic features or associated anomalies. Examination of the genital tubercle starts with careful inspection of the phallic structure, noting length, breadth, and amount of erectile tissue; number of orifices in the perineum and their topography; rugation; pigmentation and fusion of the labioscrotal folds; and position and patency of the anus (females with cloacal anomalies often have some degree of genital ambiguity). Asymmetry is also an important sign to look for, since the degree of virilization will usually follow the ipsilateral gonad; hence, some DSD conditions, like ovotesticular DSD and mixed gonadal dysgenesis (MGD), will produce virilization on only one side of the genitalia.[30] Palpation of gonads is a key step in the initial assessment. Gonads can be palpated within the scrotum or labioscrotal folds, or in the inguinal canal, or be nonpalpable. The status of the gonads on palpation bears a particularly important weight on the initial diagnostic thought process.

An accurate description of the genital tubercle is usually hampered by subjective criteria and lack of standardization. Most authors refer to the external genitalia of patients with genital ambiguity as displaying a virilized female or undervirilized male appearance, as depicted in Figure 70.3.

In either case, it is important to palpate the phallus for the presence of corpora (erectile tissue) and measure its stretched dorsal length, which can be compared with normatized data.[31]

Virilized female genitalia will usually exhibit variable degrees of clitoromegaly, pigmentation, and rugation of the labial skin and labial fusion; depending on the degree of virilization, only one opening other than the anus will be visible in the perineum, representing an urogenital sinus (UGS). The UGS represents a common channel of variable length for the urinary and genital tracts. The terms *low* (closer to the perineum) and *high* (closer to the bladder neck) are used to describe the level of the confluence between the urethra and vagina. In cases with a high confluence, the urethra is usually very short (<1.5 cm). Traditionally, the Prader classification has been widely used in an attempt to standardize such findings. It ranges from 1 (mild clitoromegaly) through to 5 (complete virilization with UGS opening up at the tip of the phallus). Figure 70.4 depicts a schematic illustration of the Prader

FIGURE 70.3 Examples of the most common DSD clinical presentations—undervirilized male or virilized female.

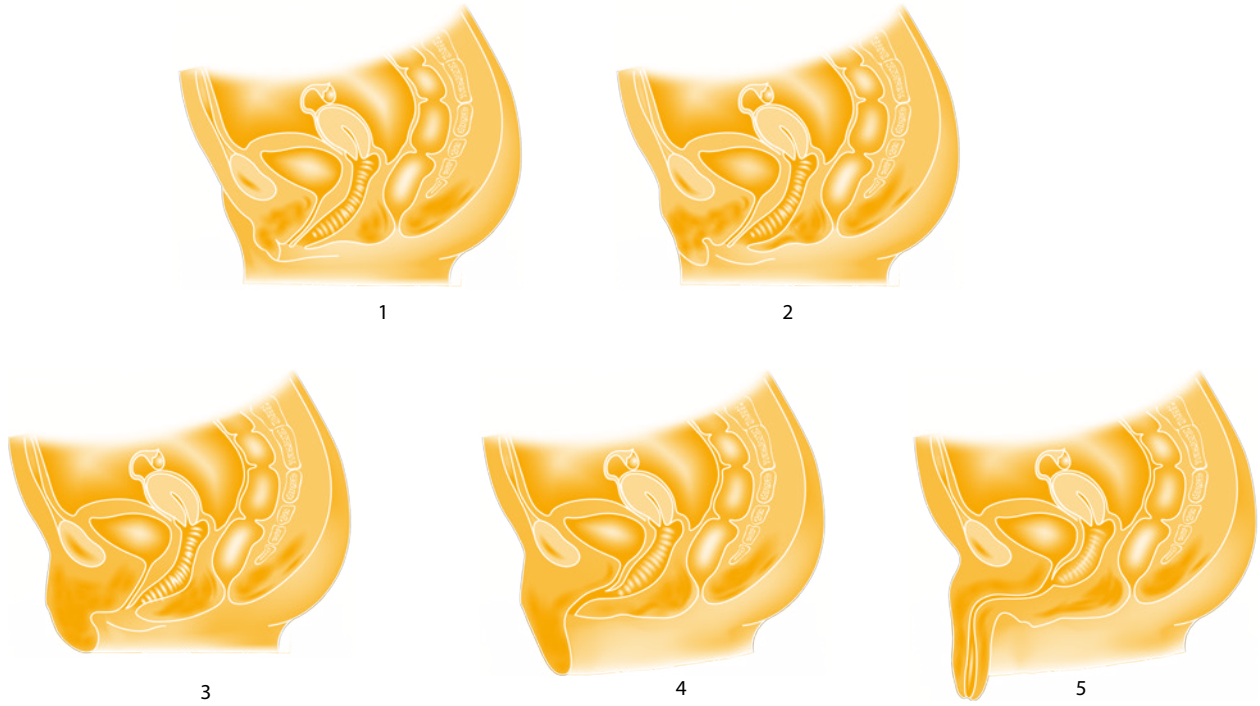

FIGURE 70.4 Schematic illustration of the Prader classification.

classification, and Figures 70.5 through 70.8 provide clinical examples of the Prader scale. The disadvantage of the Prader classification is the assumption that there is a fixed association between the external appearance of the genitalia and the internal anatomy. In other words, sometimes a severely virilized genital tubercle can be associated with a low UGS and vice versa. An alternative standardization for the description of the virilized genital tubercle, known as PVE, has been suggested. P refers to the length and width of the phallus, V relates to the distance between the entry point of the vagina in the UGS and the bladder neck and the length of the common channel measured by endoscopy, and E is the Prader number.[32] Albeit more objective, this classification has not been incorporated into clinical practice by many centers.

FIGURE 70.5 Prader 2: Mild clitoromegaly with urethral and vaginal openings clearly separate on inspection.

FIGURE 70.6 Prader 3: Moderate clitoromegaly, but separate urethral and vaginal openings are still visible or the confluence is very low (close to the perineum).

Male undervirilization is portrayed by variable degrees of hypospadias (urethral opening in the ventral aspect of the penile shaft), which can also be associated with bifid scrotum, penile ventral curvature, and penoscrotal transposition. Similarly to the PVE system described above, a score system has been proposed for cases of undervirilization in order to standardize reports and allow comparisons between different centers. According to this system, external and internal masculinization scores (EMS and IMS, respectively) are generated, taking into account all the physical examination findings that have been mentioned.[33]

FIGURE 70.7 Prader 4: More significant clitoromegaly, labial fusion, and single perineal opening.

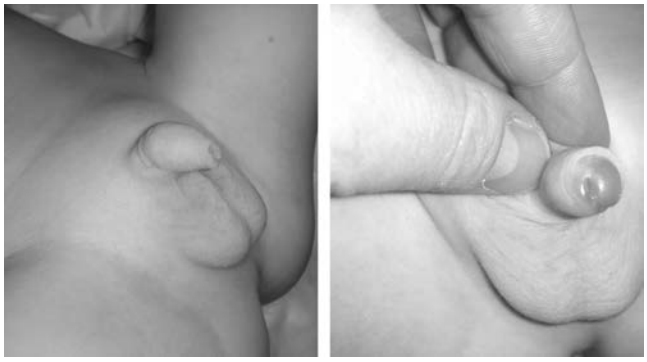

FIGURE 70.8 Prader 5: Note the undistinguishable appearance from male external genitalia and the UGS opening at the tip of the phallus.

Even in patients with normal-appearing male genitalia, a stretched penis shorter than 2–2.5 cm with a narrow breadth should be considered a micropenis and warrants further investigation.

In recent years, a rather simple measurement has been increasingly incorporated into clinical practice, the anogenital distance (AGD). It is regarded as a surrogate of androgen action and a permanent readout of the virilization process that occurred during fetal life. AGD is measured from the center of the anus to the base of the scrotum in males and to the posterior fourchette in females, and the normal male-to-female ratio is 2:1. Normative data for males and females up to 2 years old are available.[34] AGD has been demonstrated to be significantly lower in boys with hypospadias and adult men with infertility than in controls.[35,36] In females, a ratio between AGD and the distance between the anus and the base of the clitoris larger than 0.5 has been associated with severe virilization.

Diagnostic Tests

The most important initial diagnostic tests in the DSD workup are karyotype, pelvic ultrasound to evaluate the presence of Mullerian structures, and serum levels of sodium, potassium, and 17-hydroxyprogesterone (17OHP) after day 3 of life. A thorough history and physical examination (especially gonad palpation) coupled with the results of the aforementioned tests will allow the patient to be situated within the DSD umbrella, as well as receive a final diagnosis based on pathophysiology in the majority of cases. Other serum biochemistry tests frequently employed are androgen (testosterone, dihydrotesterone, and androstenedione), cortisol, gonadotropin, and AMH levels. In infants older than 3–6 months of age or if a defect of androgen production is suspected, it may be necessary to perform a stimulation test with human chorionic gonadotropin (hCG) to reliably estimate gonadal production of androgens. The availability of more advanced genomic technologies, such as genome-wide arrays to detect copy number variations and DNA sequencing at affordable prices, has exerted a positive impact on the assessment of patients with a suspected DSD, and this trend is likely to rise in the near future.[37]

Pathology reports from gonadal biopsies or removal may be helpful in formulating a more complete diagnosis, but such procedures are rarely performed in young newborns or infants right from the outset.

In the next sections, as each diagnosis is addressed individually, the constellation of clinical, genetic, and biochemical findings is detailed as well.

XX DSD (FORMER FEMALE PSEUDOHERMAPHRODITISM)

The XX DSD group can be further subcategorized into situations with androgen excess, disorders of gonadal development, and other problems (Figure 70.9).

Androgen Excess

Clinical situations where there is androgen excess leading to virilization of the female fetus can be divided according to the source of hormonal production into fetal, maternal, and placental. CAH remains by far the most common 46 XX DSD and the most frequent DSD overall.[2,20,38–40]

Congenital Adrenal Hyperplasia

CAH happens with an incidence of 1:10,000 to 1:20,000, live births.[41] The pathophysiology of CAH involves an enzymatic defect in the adrenal cortisol synthesis pathway, which leads to accumulation of precursors and excessive production of androgens (Figure 70.10). The most common enzymatic defect, which accounts for 95% of the cases, affects 21-alpha-hydroxylase (CYP21), following an autosomal recessive inheritance.[42] CYP21 has been mapped to chromosome 6. The genital tubercle shows variable degrees of virilization with bilateral *nonpalpable* gonads. Identification of Mullerian structures on US and 17OHP elevation confirm the diagnosis. Boys with this enzymatic defect do not present with genital ambiguity.

Three clinical forms of the disease are recognized. About 75% of the patients will have salt-wasting CAH, which can present with a life-threatening salt-losing crisis in the first or second week of life,[22,43] characterized by severe hyponatremic dehydration secondary to mineralocorticoid deficiency. In the simple virilizing form, residual enzymatic activity is enough for mineralocorticoid production, and nonclassic CAH is characterized by normal genitalia at

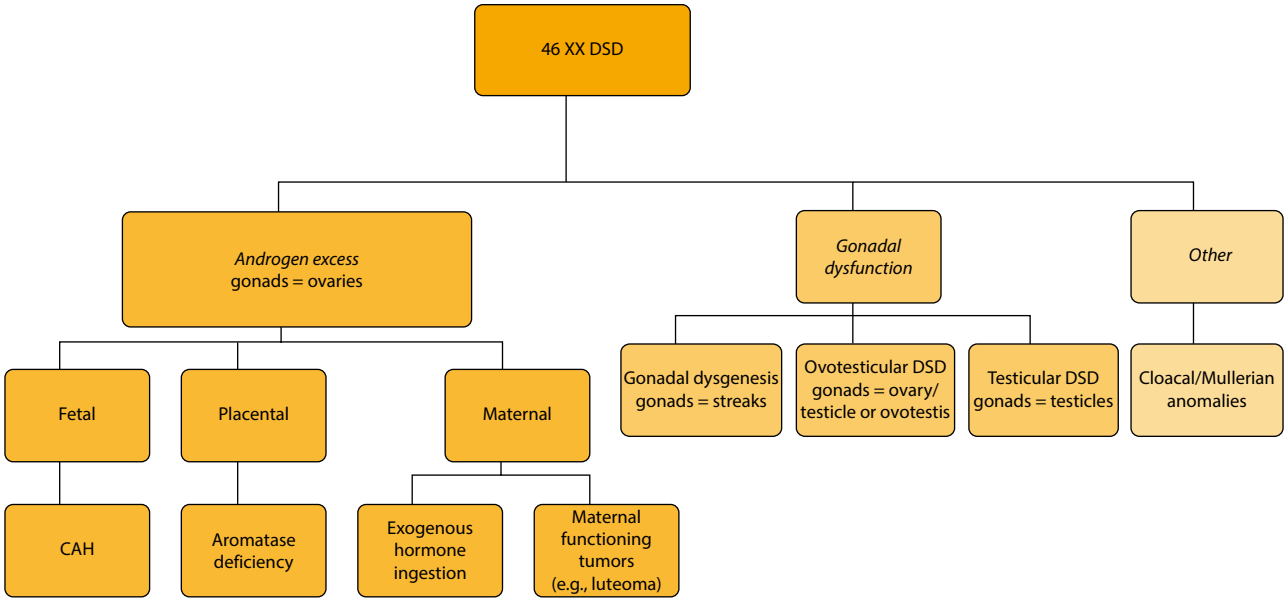

FIGURE 70.9 Diagram illustrating different causes of 46 XX DSD and the respective gonads seen with each cause.

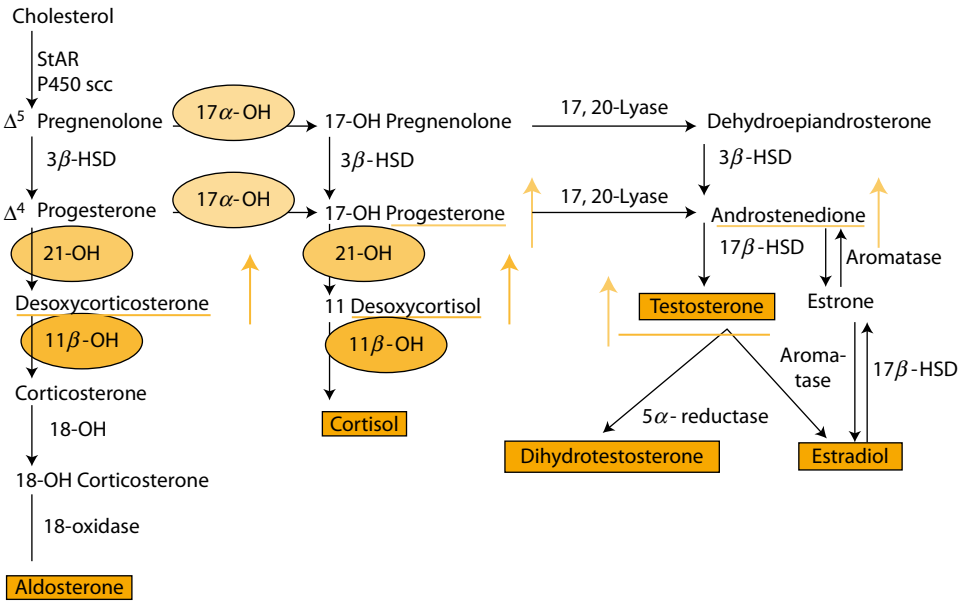

FIGURE 70.10 Cortisol synthesis pathway. The possible enzymatic defects seen with CAH are highlighted, as well as the precursors that accumulate, allowing for accurate diagnostic suspicion to be made.

birth and the onset of virilization at puberty. Although accurate determination of the type of CYP21 mutation in CAH often demands quite extensive genetic analysis due to rather complex genetic variations,[44] a high concordance rate between genotype and phenotype has been suggested; i.e., patients who are completely homozygous for a mutation (null genotype) usually have no enzyme activity whatsoever and present with severe virilization and salt-wasting disease. Conversely, patients who are compound heterozygotes for the mutations have variable degrees of residual enzymatic activity, which correlates with a milder phenotype (simple virilizing or nonclassical CAH). Interestingly, the salt-wasting form of CAH is usually associated with both the null genotype or the less severe I2 splice mutations; whereas the clinical presentation is similar for patients with either genotype, it has been demonstrated that patients with the null genotype are unique and significantly different from all the other groups in terms of gender role, sexual orientation, and psychosocial aspects (see below).[42,45] Newborn screening for 21-hydroxylase deficiency is available in many countries and allows diagnosis of CAH prior to a significant salt-wasting event.

Prenatal Treatment

Prenatal treatment of fetuses at risk for salt-wasting and simple virilizing CAH with dexamethasone remains highly controversial. The discussion does not apply to the nonclassic form of the disease. The possibility of reliably

determining fetal sex with noninvasive techniques (cell-free fetal Y DNA detected in maternal blood) as early as 4 weeks postconception holds promise, since it could allow significant reduction in unnecessary exposure to dexamethasone from seven in eight to three in four (female only) fetuses.[23] Yet, in the best-case scenario with the availability of early determination of fetal sex and amniocentesis for diagnostic confirmation at 14 weeks of gestation, three girls would be exposed to dexamethasone unnecessarily for 9–10 weeks. A recent systematic review[46] concluded that most studies on prenatal treatment are observational with low methodological quality. While the data suggest that prenatal treatment is successful in reducing virilization with no significant short-term side effects to the fetus or the mother, some degree of behavioral changes in children exposed to dexamethasone during pregnancy have been suggested and need to be investigated further before making any firm recommendations.[47] Prenatal treatment for CAH should still be regarded as experimental and discussed with families on an individual basis, with clear explanation of risks and benefits.[43]

Medical Management

Glucocorticoid replacement with the goals of replenishing the lack of cortisol and suppressing excessive androgen production by means of negative feedback on adrenocorticotropic hormone (ACTH) release remains the mainstay of medical therapy for CAH. Hydrocortisone is the preferred drug in children due to its short half-life, and it should be administered as crushed tablets.[41,43] Typical doses are in the range of 10–15 mg/m^2/day, with lower-range doses in toddlers and higher ones in adolescents.

Approximately three-fourths of the CAH population will have the classic salt-wasting form of the disease and also require mineralocorticoid replacement, in the form of fludrocortisone.

In adults, longer-acting and more potent drugs, such as dexamethasone or prednisone, are favored, since growth-suppressive effects are less relevant.

Currently, bilateral adrenalectomy is not part of the standard of care and should be considered only in cases of failed medical management, particularly in adult females with salt-wasting CAH and infertility, where compliance to medical treatment is not an issue.

Therapy is monitored through determination of morning blood levels of 17OHP and androstenedione. 17OHP reflects ACTH suppression, and complete normalization usually reflects overtreatment leading to hypercortisolism, which is also deleterious. In children, height and weight should be recorded in each follow-up visit, and a bone age should be performed yearly.[41,43] Patients with salt-wasting CAH also require Na, K, and renin monitoring.

A stress dose of steroids should be given in cases of febrile illness, dehydration, surgery, and trauma. Emotional or mental stress, as well as minor illnesses, does not require a stress dose.[43]

Gender Assignment

The DSD consensus supports female gender assignment for XX CAH patients, since more than 90% of those patients identify themselves as females[1,2] and the presence of normal female internal genitalia offers the potential for fertility. Furthermore, the incidence of gender dysphoria in adult CAH females was shown to be around 5%, which despite being a higher rate than what is found in the general population, was deemed to be acceptable to support a uniform female sex of rearing assignment in this population.[48] However, recent publications have questioned this practice for markedly virilized patients (namely Prader 5 and some Prader 4) and suggested that male gender assignment should be entertained in this particular situation.[49] A series of 12 XX CAH patients referred later in life assigned male gender demonstrated satisfactory male sexual function.[50] The topic is controversial, and at this stage, it is reasonable to state that the vast majority of XX CAH patients should be assigned females.

Timing of surgery

The timing and magnitude of surgical treatment for CAH have been a subject for intense debate in recent years. Surgical treatment for females with CAH involves feminizing genitoplasty, in the form of clitoroplasty and labioplasty, and vaginoplasty, which may be performed concomitantly or not, with the goal of exteriorizing the vagina and creating two separate openings for urethra and vagina.

Controversies surrounding the ideal timing for surgery (early infancy, i.e., first 6 months of life, vs. postpubertal) on the external genitalia have been raised and are truly unsettled. The DSD consensus, as well as the Endocrine Society CAH guidelines, recommends that for severely virilized females (Prader 3 and above), clitoral and perineal surgery should be offered in infancy, as long as performed by an experienced surgeon in a center where multidisciplinary care and psychosocial support to parents are available.[1,43]

A pro of early infancy surgery is normalization of the appearance of the external genitalia in accordance with the assigned female gender, which is the main reason driving parents to decide for this option. There is a perception that the girl left with a nonoperated virilized genitalia may go through unwarranted social interactions with her peers, leading to embarrassment and social withdrawal. Furthermore, the idea of "doing nothing" sometimes represents a stressful concept for some parents who have difficulties coping with the appearance of their child's genitalia. Lastly, notwithstanding the limited experience, some surgeons perceive feminizing genitoplasty in postpubertal girls as being technically more demanding.[51]

The main disadvantage of early surgery is that it excludes the patient from the decision to intervene and provide her own informed consent;[52] also, it is inherently associated with potential complications that are not amenable to diagnosis until later in life, such as decreased clitoral sensitivity and vaginal stenosis.

Scientific evidence supporting one or the other is faint.[3] Studies comparing parental anxiety or surgical results and perceptions by patients operated on early versus late have not been done, and the long time span needed to be able to measure outcomes poses an important methodological challenge. Long-term outcome studies of surgical intervention for CAH are scarce and often refer to surgical procedures that are outdated. Some reports suggest poor cosmetic and functional results of genitoplasty done in infancy,[53,54] with a high reintervention rate in adulthood

(especially due to vaginal stenosis[55]). A few publications have demonstrated that psychosexual outcomes in CAH patients are worse than in controls.[42,56] However, they do not seem to be necessarily related to surgical interventions, since the presence of a null genotype has been associated with poorer outcomes regardless of type of surgical treatment;[45] interestingly, most women in such reports, when questioned about the ideal timing for surgery, favor having surgery performed early in life.[45,56–58]

The authors favor that feminizing surgery should *not* be offered to girls with mild virilization (Prader 1 or 2 and some Prader 3). For those with Prader 4 or 5, surgery should only be performed after extensive discussion with the multidisciplinary team and active participation by families in the decision-making process. Regardless of the decision to perform surgery or not, parents should be under solid and continuous psychosocial support.

Since the vagina has no function in early childhood, vaginoplasty could be postponed until after puberty. The advantages of such an approach would be the inclusion of the patient in the informed consent process and assurance of cooperation for vaginal dilatations, if necessary. In addition, manipulation of the vagina is easier in the setting of higher estrogen levels. On the other hand, by not performing vaginoplasty at the time of clitoroplasty, the flaps from the UGS and prepuce would be discarded, and therefore would no longer be available for reconstruction of the distal vagina, which could represent a problem, especially in cases of high UGS or very small vaginas.

Technique

From a technical standpoint, feminizing surgery includes clitoroplasty or labioplasty and vaginoplasty. Procedures have evolved significantly in the past decade. In general, higher degrees of external virilization (Prader 4 and 5) are associated with a longer UGS and a higher insertion of the vagina. Occasionally, patients with severe virilization will have a low confluence and vice versa, so the surgeon should gather as much information as possible preoperatively to avoid surprises. That can be achieved through a genitogram performed with contrast injection in a retrograde fashion through the UGS and pan-endoscopy (cystoscopy or vaginoscopy) in the operating room to assess the length of the common channel and the level where the vagina enters the UGS.

CLITOROPLASTY

The first report of clitoroplasty (as opposed to clitoral amputation) for patients with enlarged clitoris dates back to the 1960s.[59] Later on, more elaborate techniques aimed at preserving the dorsal neurovascular bundle, and thus sensation, were described.[60,61] The procedure starts with a circumcision, followed by degloving that mirrors what is done for hypospadias repairs (Figure 70.11). The dorsal foreskin is split longitudinally, and the flaps obtained are used for labia minora reconstruction. Most authors suggest subtunical removal of erectile (corporal) tissue ventrally, sparing the glans with its neurovascular supply (Figure 70.12). After dissection is completed, the proximal aspect of the corporal bodies at the level of the crura

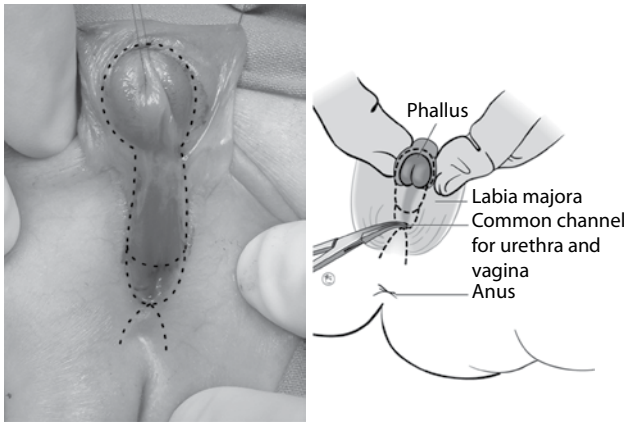

FIGURE 70.11 Outline of the initial incision for feminizing genitoplasty.

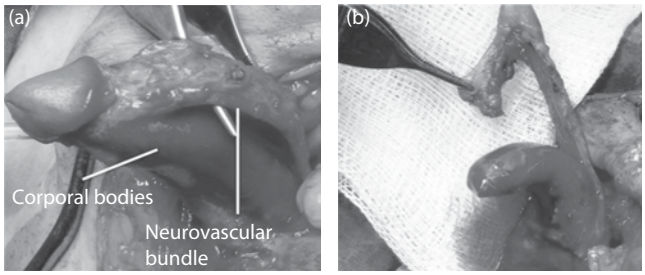

FIGURE 70.12 (a and b) Dissection of the clitoral corporal bodies from the dorsal neurovascular bundle.

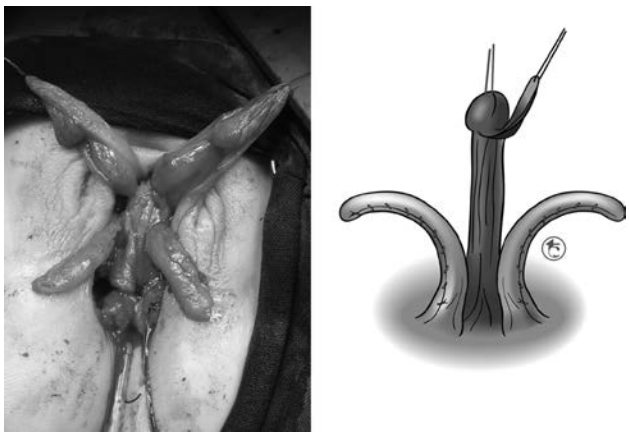

FIGURE 70.13 Dissection is complete. Neurovascular bundle and glans and corporal bodies are independent units.

is controlled with suture ligation for hemostasis, and the clitoris is receded with a stitch to the periosteum of the pubic bone. Maintenance of the dorsal clitoral skin is crucial since it has been demonstrated in healthy women that the clitoris and area above it are the key areas to achieve orgasm.[62] The scrotal-type skin is used for labia majora reconstruction. A corporal-sparing clitoroplasty where no tissue is ablated from the clitoris has been described, with the goal of preserving all sensation-bearing structures,[63] where the corporal bodies are separated and kept in a subcutaneous pouch after labial reconstruction (Figures 70.13

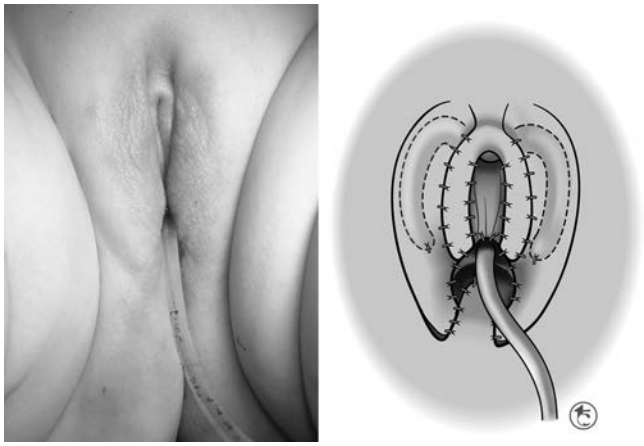

FIGURE 70.14 Final aspect of a feminizing genitoplasty. Note the schematic representation of corporal bodies spared and tacked to a subcutaneous pouch on either side.

and 70.14). In instances where the glans is too prominent, glans reduction can be done either by wedge resection or by deepithelization.[64]

VAGINOPLASTY

The choice of technique for vaginoplasty is contingent on the site where the vagina opens into the UGS. Some reports have suggested that a common channel of ≤3 cm would be the cutoff between a high and a low vaginal opening.[65] Others (including the authors) have implied that the distance between the urethrovaginal confluence and the bladder neck is in fact more important than the length of the common channel.[66,67] Figures 70.15 through 70.17 exemplify possible relationships between the urethra and vagina in a UGS. From a surgical perspective, techniques range from flap vaginoplasties (Fortunoff and Passerini–Glazel) to vaginal pull-through after complete separation from the UGS, going through total and partial urogenital mobilization.

With the flap techniques, a perineal skin flap is used to bridge the gap between the vagina and the perineum. The Fortunoff flap was described in 1964 and consists of an inverted U-shaped incision in the perineum that is elevated as a flap and sutured to the posterior wall of the vagina.[68] In the Passerini–Glazel technique, the vagina is disconnected from the UGS and the so-called mucocutaneous plate from the UGS is tubularized and anastomosed to the vagina.[69] When flap techniques are utilized, only the posterior vaginal wall is mobilized. The actual anterior vaginal wall is never mobilized, and a mucocutaneous flap of UGS is required to bridge the gap between the hypospadiac urethra and the perineum; the result is a simple augmentation of the UGS diameter. For a long time, flap vaginoplasties were widely employed even for the high UGS, since they were the only available alternatives, which probably explains the high reported incidence of vaginal stenosis requiring reintervention in some series.[42,55]

In the last two decades, total and partial urogenital sinus mobilization (TUM and PUM, respectively) have been introduced to the surgical armamentarium

FIGURE 70.15 Genitogram demonstrating an intermediate confluence between the urethra and vagina—the common channel extends until the midportion of the urethra where the vagina enters.

FIGURE 70.16 Genitogram demonstrating a very low UGS. It is likely that upon inspection of the genitalia with gentle traction of the labia, one would be able to visualize separate openings.

FIGURE 70.17 Example of a very high UGS. The vagina enters the common channel almost at the level of the bladder neck. Note that the UGS resembles the male urethra.

of vaginoplasties as a technical variation of the surgical approach to cloacal repairs described by Peña.[70] He observed that patients with cloacal anomalies that underwent extensive repairs where separation of the rectum, vagina, and urethra was attempted commonly developed complications related to the urogenital portion of the procedure, namely, urethrovaginal fistulas. He described total mobilization of the UGS as a unit (TUM) in order to minimize those complications, and following that, other authors expanded on the indication to include vaginoplasty in CAH patients.[65] TUM seems to produce better results than flap vaginoplasties, especially in low UGS.[71] Nonetheless, the problem of high vagina remains, due to the need of extensive mobilization, which is concerning for the possibility of disrupting the urinary continence mechanism by placing undue traction on the bladder neck. To limit such potential disruption, PUM was devised, where the same principles of TUM are followed, except that the pubourethral ligaments are not incised.[72,73] A recent comparison between the two techniques in terms of urinary continence showed no difference after 4 years of follow-up.[74] However, long-term follow-up is definitely warranted, especially after situations like pregnancy and delivery, to ensure no urinary functional issues will arise. In both techniques, the excess mucosa from the UGS after mobilization can be used to create a mucosa-lined vestibule.[66]

As outlined above, the most challenging aspect of the surgical treatment of CAH is the vagina with high insertion in a long UGS. Although flap vaginoplasties have been widely employed even in this scenario, in our view, the best approach for such cases is a vaginal pull-through, where the vagina is disconnected from the UGS, which in turn will be kept as a urethra, and mobilized to the perineum. This technique was initially described using an anterior perineal approach,[75] which proved to be quite technically demanding and was later replaced by a posterior sagittal approach, similarly to what is done for anorectal malformations, with a protective colostomy.[76] In recent years, the anterior sagittal transrectal approach (ASTRA) was introduced;[77] in this technique, only the anterior wall of the rectum is opened longitudinally, with the patient in the prone position, allowing the high vagina to be separated from the urethra and mobilized to the perineum with improved exposure in a more ergonomic way for the surgeon (Figure 70.18a and b). In our view, the ASTRA approach offers better exposure, facilitating the dissection and separation of the vagina from the UGS[67] without the need for a colostomy or extensive bowel preparation. Others have suggested that the vaginal pull-through can be performed without opening the rectum, as long as the patient is placed in a prone position.[66] Despite the improved exposure, dissection and mobilization of the vagina in the infant can be challenging given its inherent friability. The use of topical estrogens on the genitalia

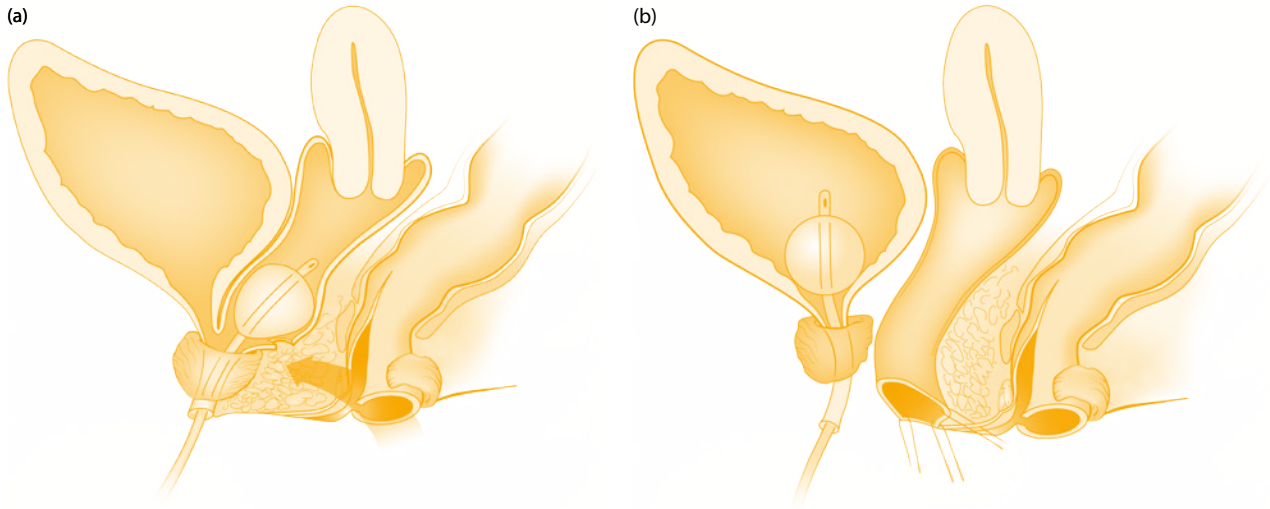

FIGURE 70.18 (a and b) Schematic illustration of the transrectal approach for the high vagina (ASTRA).

4 weeks before surgery in this age group, with the goal of increasing the robustness of the genital structures for surgical manipulation, has produced encouraging preliminary results. Many patients undergoing vaginoplasty in infancy will require dilatations or minor procedures after puberty; however, repeated interventions in the prepubertal patient should be avoided.

Maternal and Placental Causes of Androgen Excess

The most common maternal cause of virilization is exogenous administration of androgenic drugs. Whenever there is a history of maternal virilization (development of acne, voice changes, and clitoromegaly) during pregnancy, the possibility of placental aromatase deficiency and, rarely, maternal androgen-secreting tumors, such as luteomas, should be entertained.[1,22,78] In these situations, maternal testosterone is usually high and estradiol low. After birth, withdrawal of the androgenic stimulus may lead to significant reduction in clitoral size, which justifies taking an initial conservative approach in such cases.

Disorders of Gonadal Development

This category encompasses problems of ovarian development. Included in this subcategory are ovotesticular DSD, gonadal dysgenesis, and testicular DSD. 46 XX gonadal dysgenesis is exceedingly rare and not seen in infancy, since there is no genital ambiguity. Testicular and ovotesticular DSDs can share common genetic features, and the concomitant reported occurrence in monozygotic twins suggests a possible common origin.[79] In more than 80% of the testicular DSD patients, a translocated copy of the SRY gene is identified in the X paternal chromosome;[80] in contrast, only 10% of ovotesticular DSD patients are SRY+.[81]

Ovotesticular DSD

Ovotesticular DSD replaced the term *true hermaphroditism* and is defined by the presence of normal ovarian tissue containing follicles and normal testicular tissue containing tubules in the same individual. The tissues can be present within the same gonad (ovotestis) or independently (ovary and testicle). The most common gonadal combination is ovotestis–ovary, followed by ovotestis–ovotestis, ovary–testis, and less frequently, ovotestis–testis.[81] The occurrence of ovotesticular DSD is quite rare.[20,21] Patients with this entity usually present with genital ambiguity and marked asymmetry of the external genitalia (Figure 70.19). Associated inguinal hernia is common. The most common karyotype is 46 XX (about 60% of the cases), followed by mosaicism containing a Y chromosome (25%) and XY (15%). Gender assignment decisions are individualized based on the appearance of the external genitalia, hormonal profile, and response to hCG and are usually split equally between male and female gender.[82,83] Surgical treatment will entail removal of discordant gonadal tissue and other structures to the sex of rearing. The same controversy presented before in terms of timing of genital surgery exists, and psychosocial support to patients and families is paramount, as in any other type of DSD.

FIGURE 70.19 Example of significant asymmetry of the external genitalia on inspection.

Testicular DSD

Most patients (80%) with 46 XX testicular DSD (formerly called "XX male") present after puberty with normal genitalia, pubic hair, small testes, and gynecomastia. They are usually infertile men due to azoospermia that demonstrate hypergonadotropic hypogonadism biochemically. The remainder usually present at birth with ambiguous genitalia.[80]

Other Causes

Miscellaneous rare conditions, also called nonhormonal DSDs, are included in this subcategory. Examples are cloacal and Mullerian anomalies. Cloacal anomalies, including cloacal exstrophy, will be covered in Chapter 73. It should be kept in mind that a newborn baby with an ambiguous genitalia and a single perineal opening is a female with a cloacal anomaly until proven otherwise (Figure 70.20).

FIGURE 70.20 Newborn with cloacal anomaly and virilized appearance of external genitalia.

XY DSD (FORMER MALE PSEUDOHERMAPHRODITISM)

XY DSD is a more diverse and heterogeneous group than XX DSD. The success rate in establishing the precise pathophysiology and etiology of 46 XY DSD is far lower than that in XX DSD (Figure 70.21).[2] Furthermore, this category encompasses a wider range of diagnoses where genital ambiguity is not necessarily present. Finally, gender assignment discordant to karyotype (i.e., female assignment) is prevalent in this group. Similarly to XX DSD, the XY group can be subcategorized in disorders of gonadal (testicular) development, androgen synthesis, androgen action, and other problems (Figure 70.1).

Disorders of Androgen Action

Partial Androgen Insensitivity Syndrome

The vast majority of patients in the XY DSD group will present with variable degrees of undervirilization despite normal androgen production by the pituitary–gonadal axis, normal AMH function (depicted by the absence of Mullerian structures), and normal testicular histology. Several mutations in the AR have been identified that can lead to variable degrees of androgen insensitivity syndrome;[84] however, the most optimistic reports estimate that no more than 50% of cases of undervirilization will have an identifiable AR mutation,[8] and a precise etiology remains undefined for most of them. Although the term *partial androgen insensitivity syndrome* (PAIS) is used interchangeably both for patients with and those without a proven AR mutation, most authors agree on the inadequacy of the term PAIS when the mutation is not confirmed. Recent studies have pointed out mutations in the Mastermind-like domain containing 1 (MAMLD1) as an additional possible etiology for PAIS-like phenotypes with a normal AR.[8,85]

Environmental endocrine disruptor chemicals (EDCs) have also been related to the rising incidence of hypospadias, cryptorchidism, and male infertility in the general population.[86]

Since the yield of diagnostic studies is so low and potentially costly, a question that is pertinent to the pediatric urologist is, which patients deserve to be investigated? Patients that are not considered to have ambiguous genitalia per se, with common conditions such as hypospadias or bilateral undescended testicles, will commonly be referred for surgical treatment, and drawing the line of which patients will truly benefit from additional genetic and biochemical testing can be rather challenging. Traditionally, the 2/3 rule has been taught, where the phallus and each gonad represent a unit and abnormalities in two out of three (e.g., hypospadias and one undescended testicle, or normal phallus with two nonpalpable testicles) would warrant further investigation. Approximately 1/3 of patients with proximal hypospadias and at least one undescended testicle have an abnormal karyotype, but the yield is lower if patients with distal hypospadias are included.[87] Furthermore, it seems that a nonpalpable gonad is more predictive than a palpable one when the association of hypospadias and undescended testicle is studied for the presence of a DSD condition.[88] Albeit the consensus advocates for a full DSD workup for patients with perineal hypospadias and bilateral descended testicles,[1,2] a review of the authors' data showed that the large cohort of such patients with well-developed phallus and scrotum with 46 XY karyotype was uniformly assigned male and found not to harbor any Mullerian structures. Therefore, it seems that labeling such patients as having "ambiguous genitalia" is inappropriate, and lengthy delays in sex assignment for such patients should be avoided, as this is a significant source of stress for parents and has no impact on the management.[89]

Gender Assignment

In patients with PAIS and PAIS-like phenotypes, gender assignment can be rather challenging in the setting of significant undervirilization and a small phallus. Recent studies have documented the existence of a masculinization

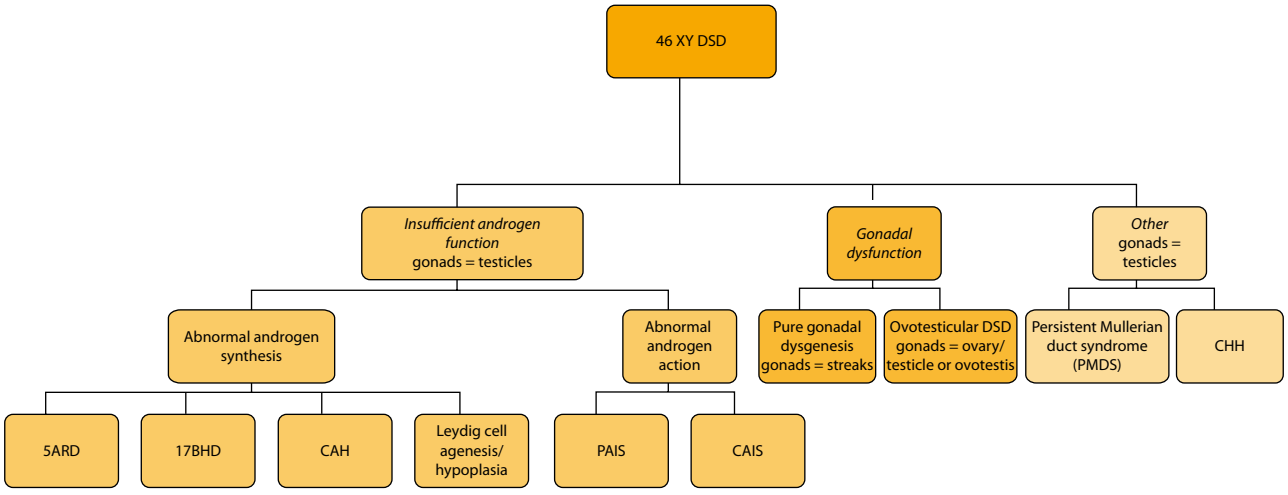

FIGURE 70.21 Diagram illustrating differential diagnoses for XY DSD. 5ARD, 5-alpha-reductase deficiency; 17BHD, 17-beta-hydroxysteroid dehydrogenase deficiency.

programming window, i.e., a critical moment of androgen exposure prenatally; interestingly, although this window, believed to take place between 8 and 12 weeks of gestation, seems vital for penile development and growth, at 14 weeks there is not a significant difference between the size and appearance of the clitoris and the penis. Therefore, it has been hypothesized that the masculinization window is key for brain imprinting and development of a male identity.[90] In fact, it could explain the male gender role adopted by some CAH patients with severe virilization (possibly the ones bearing the null genotype), i.e., early exposure to androgens during development. Postnatally, there is another period of surge in luteinizing hormone (LH) and testosterone that seems important to ensure penile growth to full potential.

In the past, severely undervirilized XY patients were offered feminizing surgery, gonadectomy, and hormonal replacement as part of the "optimal gender approach," which was based on the assumption that sex of rearing would overrule chromosomal or gonadal sex ("nurture over nature").[30,91] This concept has been challenged in face of long-term outcomes studies suggesting that XY DSD patients are usually satisfied and lead a well-adjusted sexual life regardless of their sex assignment.[91,92] Partially virilized XY females demonstrate the highest rates of gender dysphoria and need for reassignment among all patients with a DSD, as well as dissatisfaction with surgical interventions.[93] Therefore, patients with at least one functional testicle and reasonable penile tissue on palpation should be raised as males.[50,94] A stimulation test with hCG can estimate the ability of the testicle to produce testosterone by assessing the response of the external genitalia. When there is poor production of testosterone by the testis, exogenous administration is warranted. Patients with very poor response to testosterone remain a difficult group to assign, and a multidisciplinary decision is essential.

If male gender is assigned, surgical management will usually entail orchidopexy and hypospadias repair, topics that will be covered in other chapters.

Complete Androgen Insensitivity Syndrome

Patients with CAIS do not present with genital ambiguity. A mutation in the AR is identified in up to 80% of patients with CAIS.[84] Such mutations are transmitted following an X-linked pattern; i.e., females are carriers, whereas males develop clinical manifestations. Complete absence of androgen action precludes any virilization of the external genitalia. Patients with CAIS are usually diagnosed in infancy or childhood when a testicle is palpated or found in the groin during an assessment or exploration for an inguinal hernia in an otherwise phenotypically normal female (Figure 70.22). Another possible clinical presentation is primary amenorrhea at puberty. These patients usually have a male-typical androgen profile, commonly responding with significant elevation in testosterone levels after stimulation and no identifiable Mullerian structures. Most CAIS patients are being raised as females at the time of diagnosis, so gender assignment is not commonly an issue. About 60% of CAIS patients develop Wolffian structures (vas deferens and seminal vesicles) due to a paracrine effect of testosterone.

FIGURE 70.22 Testicle identified in the inguinal canal during a hernia repair in a phenotypically normal female with CAIS.

Historically, these patients underwent gonadectomy soon after diagnosis, due to an increased risk for germ cell malignancies, followed by lifelong hormonal replacement to induce pubertal changes and development of secondary sexual characteristics. The exact risk of malignancy in patients with CAIS is not well known, but is clearly above that in the general population.[95] Since the gonads are not dysgenetic and most patients with testicles in situ will experience spontaneous puberty secondary to conversion of testosterone into estrogen through aromatization, a case has been made for delaying gonadectomy at least until puberty is complete.[96] Furthermore, recent reports challenge the need to perform gonadectomy at all, since there have been anecdotal reports of loss of libido following gonadectomy. In addition, concerns have been raised around long-term hormonal replacement and even the potential of the gonads harboring viable germ cells that could be used for fertility purposes in the future with advanced technology.[95] Appropriate follow-up modalities and screening intervals for gonadal tumors have not yet been delineated, as most patients have undergone gonadectomy at the time of diagnosis or after the completion of puberty. In postpubertal patients who choose to retain the gonads, surveillance with yearly ultrasounds is strongly advised.[95]

CAIS patients usually have a short, blind-ending vagina; procedures that may be required to ensure proper intercourse range from simple dilatations to more complex reconstructive procedures, like sigmoid vaginoplasty.[97] Such interventions should only be offered to patients who are motivated to engage in sexual activities, and therefore comply with the need of postoperative dilatations. Despite being well adjusted as females based on long-term follow-up studies,[92] high rates of dissatisfaction with sexual activity have been reported in this patient population, underscoring the importance of long-term psychological support.[93]

Disorders of Androgen Synthesis

Included in this subcategory are 5-alpha-reductase and 17-beta-hydroxysteroid dehydrogenase deficiencies, some rare forms of CAH (3-beta-hydroxysteroid dehydrogenase

and 17-alpha-hydroxylase deficiency), Leydig cell agenesis or hypoplasia (associated with LH receptor mutations), and other exceptionally rare enzymatic defects.

5-Alpha-Reductase and 17-Beta-Hydroxysteroid Dehydrogenase Deficiencies

These enzymatic deficiencies represent disruptions of the final pathways of androgen synthesis in the testis. 5-Alpha-reductase is composed of two isoenzymes, and SRDA2 is responsible for conversion of testosterone into DHT. Deficiency of this enzyme will usually lead to variable clinical features of genital ambiguity, but complete female phenotypes or isolated micropenis is also possible.[98] Along with PAIS, SRDA2 deficiency is part of the differential diagnosis for undervirilization in patients with a normal pituitary–gonadal axis (i.e., normal gonadotropins and testosterone levels). The diagnosis is suspected due to an abnormally high T/DHT ratio, with several mutations being described. Interestingly, the analysis of a large cohort of patients with XY DSD and normal testosterone production yielded a mutation in the AR in 42.5%; however, new polymorphisms associated with mutations in the SRD5A2 gene were recognized with a frequency higher than once considered (6.2%), thus explaining variable phenotypes of 46 XY DSD.[99] This finding has been corroborated by other publications that, besides identifying new mutations in SRD5A2, found a higher than previously reported incidence of mutations in XY partially virilized adult females.[100]

17-Beta-hydroxysteroid dehydrogenase isoenzyme 3 converts androstenedione to testosterone. The most common phenotype associated with abnormalities on its gene (HSD17B3) is a complete female-appearing external genitalia, although ambiguity is also possible. Diagnosis is suspected on the basis of an elevated androstenedione/testosterone ratio.

The interesting common feature shared by 5-alpha-reductase and 17-beta-hydroxysteroid dehydrogenase deficiencies is that although most patients are initially raised as females,[98] severe virilization can take place at the time of puberty, leading to self-reassignment to the male gender.[30] Hence, when the diagnosis is made in infancy, the consensus position is that strong consideration for male assignment should be given, as even the potential for fertility can be expected.[1]

CAH in XY Patients

Males with CAH due to CYP21 deficiency do not present with genital ambiguity. Nonetheless, higher infertility rates have been reported in this group than in the general population. Testicular adrenal rest tumors (TARTs), which are located in the rete testis and can cause obstruction of the seminal ducts with subsequent testicular damage, are thought to be the main cause for infertility.[43,101]

Less common enzymatic defects, such as 3-beta-hydroxysteroid dehydrogenase and 17-alpha-hydroxylase deficiencies, are examples of forms of CAH that can produce variable degrees of undervirilization due to blockage of testosterone production. Adrenal crisis is anticipated due to a lack of production of mineralocorticoids and cortisol. Such patients follow replacement protocols similar to those for females with salt-wasting CAH and require reconstructive penile procedures following the techniques described for hypospadias repairs.

Nonclassic Lipoid Congenital Adrenal Hyperplasia

Lipoid CAH is a rare autosomal recessive disorder of both adrenal and gonadal steroidogenesis. It is caused by mutations in the steroidogenic acute regulatory protein (StAR) gene and is characterized by a defect in the conversion of cholesterol into pregnenolone, leading to complete deficiency of glucocorticoids, mineralocorticoids, and sex steroids. There is a spectrum of clinical presentation, which correlates with the molecular defect. In the most severe end, XY patients depict complete sex reversal and severe adrenal crisis early in life with significantly enlarged adrenal glands on imaging studies due to cholesterol accumulation. The occurrence of less severe manifestations, including variable degrees of undervirilization and adrenal crisis with late onset, explains why even patients with a PAIS-like profile may have this disease and underscores the importance of genetic studies to enhance the understanding of DSD mechanisms and thus aid in treatment and counseling.[102]

Disorders of Testicular Development

Genes involved in normal testicular development have been described in the "Genital Development" section. These disorders will impair the ability of the testicle to produce testosterone to a variable extent, ranging from no production whatsoever (featured clinically by sex reversal) to subnormal production presenting with a spectrum of undervirilization. An overview of the different clinical situations is outlined below.

Pure Gonadal Dysgenesis: XY Sex Reversal

In pure gonadal dysgenesis (PGD), also known as Swyer's syndrome, patients are phenotypically female with normal Mullerian structures and bilateral streak gonads. These patients usually present in adolescence for primary amenorrhea. In contrast with CAIS, their testosterone levels are usually low, even after stimulation. Early gonadectomy at the time of diagnosis is advised due to the high risk of malignancy (gonadoblastoma [GB] and dysgerminoma, which have been described as early as the second decade of life[103]), and female gender assignment is a consensus.

Ovotesticular DSD

Only 15% of patients with this condition have an XY karyotype; refer to the "XX DSD" section for details.

Other XY DSDs

Persistent Mullerian Duct Syndrome

Persistent Mullerian duct syndrome (PMDS) does not present with genital ambiguity. Patients are usually males with cryptorchidism found to harbor Mullerian structures in the abdomen (uterus, cervix, and proximal third of the

vagina). It is caused by a mutation on the gene that encodes either AMH or its receptor; such mutation is transmitted following an autosomal recessive trait. Surgical removal of the Mullerian structures seems logical since malignancies have been reported and at times their attachments can hinder the performance of a tension-free orchidopexy. Removal can be achieved laparoscopically with care being taken not to damage the vas deferens.[104] When Mullerian remnants are found during an inguinal orchidopexy, the proximal aspect of the fallopian tube can be transected and removed with the uterus, leaving its distal component attached to the vas deferens, allowing the testis to be brought to a scrotal position. Such a maneuver avoids separation of the tube from the cord structures, protecting the deferential and testicular blood supply.

Causes of Micropenis Associated with Hypogonadism

Two conditions that present with micropenis with or without cryptorchidism deserve to be mentioned: congenital hypogonadotropic hypogonadism (CHH) and testis regression syndrome.

CHH presents more commonly as an isolated condition transmitted following an autosomic recessive pattern, but it can be part of a pan-hypopituitarism disorder. Moreover, CHH coupled with anosmia characterizes Kallman's syndrome, with variable patterns of inheritability being described (X linked, autosomic dominant, or recessive). CHH usually presents with isolated micropenis (without hypospadias) accompanied by cryptorchidism in the most severe form of the disease. A biochemical profile shows low levels of FSH, LH, and testosterone, but a good response to an hCG stimulation test. The cornerstone of CHH treatment is exogenous replacement of gonadotropins, which allows for reasonable penile length to be achieved.[105] Cryptorchidism, whenever present, is approached surgically without any peculiarities.

Testis regression syndrome (also referred to as bilateral vanishing testis syndrome) has a very similar clinical and biochemical profile, with the exception that testosterone levels do not respond to exogenous stimulation with hCG.[106] Testes are usually very small and undescended, and the need for their removal is somewhat controversial but favored by most given the presence of viable germ cells in roughly 10% of cases.[107] Testosterone replacement should in theory be able to drive pubertal changes, but long-term follow-up is scant.[106]

SEX CHROMOSOME DSD (MOSAIC KARYOTYPE)

This subgroup includes any DSD patient with a mosaic karyotype (Figure 70.23). It encompasses patients with Turner (45 X) and Klinefelter syndromes; the latter can be associated with genital ambiguity (usually undervirilization), although rarely so. In most patients with Klinefelter syndrome, the testicles and the pituitary–gonadal axis are normal until the onset of puberty.[108] From the DSD perspective, the main diagnosis in this group is MGD associated with a 45 X/46 XY karyotype. Interestingly, more than 90% of patients with a 45 X/46 XY karyotype

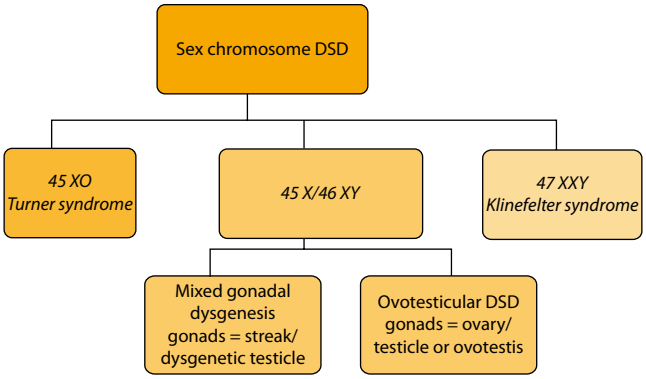

FIGURE 70.23 Diagram of the most common sex chromosome DSD situations.

detected prenatally have a normal male phenotype and present later in life with short stature and/or infertility.[28] Patients with ovotesticular DSD can also present with such karyotype (see above).

Mixed Gonadal Dysgenesis

Patients with MGD generally present with genital ambiguity, asymmetrical external genitalia, and not uncommonly, inguinal hernias. Their gonad configuration is streak or testicle. The testicular position is variable, ranging from orthotopic to intra-abdominal. The testicle can be histologically normal or dysgenetic. Intra-abdominal testes are more commonly dysgenetic.[109] It is not uncommon to see evidence of virilization only on the side where the testicle is present and Mullerian structures on the side of the streak gonad. The degree of virilization is variable and compatible with the ability of the dysgenetic testicle to produce testosterone. Similarly to ovotesticular DSD, clinical presentation (appearance of the external genitalia), as well as hormonal profile, is widely variable, which explains the reason for the absence of a formal recommendation for gender assignment, with reports approaching 50% for male and female.[21,109]

The streak gonad is at risk for GB and should be removed irrespective of the sex of rearing. In patients raised as females, the testicle should be removed as well. Conversely, it is acceptable to keep the testicle in patients raised male, as long as they can be brought to a scrotal position for surveillance, since it seems that tumor risk in this population is directly related to the degree of masculinization[110] (i.e., the more masculinized, the lower the risk of malignancy). The long-term potential for fertility is deemed as low, but exact figures remain unclear.[109]

DSD GONADS AND CANCER RISK

Virilized 46 XX DSD patients are *not* at increased risk for gonadal tumors. Nevertheless, patients with any form of gonadal dysgenesis or undervirilization can develop germ cell tumors (GCTs), which are dichotomized further into seminomatous (seminoma of the testis and dysgerminoma of the ovary or streak, which are morphologically and genetically identical[111]) and nonseminomatous, the

latter being associated with multiple variants, i.e., yolk sac tumor, teratoma, choriocarcinoma, and embryonal carcinoma.[112] The type of tumor developed will be contingent on the degree of masculinization or "testicularization" of the gonad.[111]

The precursor lesion of GCTs in testes is carcinoma in situ (CIS), also called intratubular germ cell neoplasia. Conversely, the CIS counterpart in the dysgenetic gonad with a low level of virilization (streak or ovary) is called GB. The coexistence of both precursor lesions in the same gonad is possible. Furthermore, the risk of GCT development in DSD patients seems to be directly related to the presence of a particular portion of the Y chromosome, known as the gonadoblastoma region (GBY). Currently, the candidate gene that stands out in this region is the testis-specific protein (TSPY). Characteristics that modify the risk for developing GCT apart from the presence of the GBY region are position (abdominal, inguinal, or scrotal) and state of maturation. Seminomas have been shown to be much more frequent in intra-abdominal testicles.[111]

Gonads that have accomplished more in terms of maturation (ovary, testicle, and even ovotestis) are at lower risk for tumor development than the ones retaining immature structures. The aforementioned characteristics constitute the rationale to use molecular markers for the prediction of risk of tumor development, depending on the diagnosis, clinical features, and histology of gonadal biopsies. Hence, coexpression of OCT3/4, markers of the presence of gonocytes or primordial germ cells, and TSPY flag germ cells at risk. It should be noted that germ cells may depict such markers just as a consequence of delayed maturation, which is particularly common within normal testicles in young infants, since spermatogonia only complete their development after puberty, in contrast to oogonia, which have been converted to oocytes at birth. Stem cell factor (SCF), the ligand of c-kit, seems crucial for migration and survival of primordial germ cells; however, it is not identifiable under physiologic conditions in human gonads. Remarkably, it is consistently present in testicles showing CIS and GB, but not maturation delay. Therefore, immunohistochemical staining for such markers combined with SOX9 (Sertoli cell marker) and FOXL2 (granulosa cell marker) in biopsy specimens may provide the grounds for proper risk stratification and follow-up decisions.[111]

Whenever operating on a supposedly dysgenetic gonad, careful attention should be directed to its shape, color, adnexa structures, and size. Streak gonads should be removed, and the ideal approach will be either laparoscopy or inguinotomy, depending on the location. In patients assigned male gender, Mullerian structures associated with the streak gonad can be removed simultaneously with it; however, the testicle should be preserved. If it is not in an orthotopic position, an orchidopexy should be performed. Once in a scrotal position, periodic surveillance with physical examination is advised; testicular biopsy at the time of orchidopexy and after puberty should be given consideration.[109] Whenever performing a biopsy on such testicles, a piece of tunica albuginea overlying the parenchyma should be included in the specimen, as well as blotted areas, which usually correspond to areas containing seminiferous tubules.

MULTIDISCIPLINARY APPROACH AND PSYCHOSOCIAL SUPPORT

DSDs represent a broad, complex field that requires interaction of multiple disciplines with a diverse knowledge base. One of the most significant contributions of the consensus was to bring such an assortment of professionals and patients' representatives to the same table in order to improve the care of patients with these difficult conditions, as well as provide standardization that facilitates communication between researchers.[113,114] Multidisciplinary care for DSD patients should be seen as standard and focused on the patient's best interest.[113]

Essentially, the roles in the multidisciplinary clinic should be well established: geneticists and genetic counselors have key participation in incorporating new methods for improved etiologic diagnosis, aiding insight into pathophysiological mechanisms and counseling; endocrinologists and surgeons and urologists are responsible for the central aspects of patient management; and gynecologists are key in the follow-up of teenage girls and issues related to sexuality and fertility. Participation of patient support groups in a constructive fashion[115] in forums of discussion and decisions about DSDs should be encouraged. Finally, lifelong psychosocial support cannot be underrated and is mandatory for every patient with a DSD. This support can be provided by a range of those with expertise in pediatric mental health, including social workers, psychologists, and/or psychiatrists (ideally all three). They provide support and guidance to families coping with the difficult period prior to the decision about sex of rearing, through the normal developmental transitions of childhood and adolescence, and support the move into adult care. They also provide links to peer support, whether it is through connecting families, facilitating contacts with patient support groups, or running groups for adolescents with DSDs. The benefits of such support cannot be underestimated. The clinic group may also include child life specialists, ethicists, and nurses. The multidisciplinary clinic ideally should also focus on transition from childhood into adulthood and research aspects at both the basic science (genetics and molecular biology) and clinical (long-term outcomes) levels.

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CHAPTER 71

Anorectal Malformations and Cloaca

Andrea Bischoff, William R. DeFoor, Curtis A. Sheldon, and Alberto Peña

INTRODUCTION

The pediatric urologist must be familiar with the management of anorectal malformations (ARMs) and cloacal malformations (CMs). ARMs are commonly associated with surgically relevant urinary tract and vaginal pathology. The pediatric urologist is responsible for the management of these defects. Because these malformations are relatively uncommon, it is vitally important for the reconstructive surgeon to be familiar with the anatomy and pathophysiology of each of these. Considerable morbidity ensues if the surgeon fails to manage these defects in a thoughtful, deliberate manner. A multidisciplinary approach to children with complex CMs is appropriate and involves pediatric colorectal surgeons, pediatric urologists, pediatric anesthesiologists, and pediatric radiologists.

ARMs occur in approximately 1 in 4000 to 1 in 5000 live births.[1] Cloacal anomalies occur in 1 in 50,000 live births.[2] The incidence of mortality with ARMs has dropped dramatically over time. The morbidity associated with these anomalies is extensive and includes psychosocial developmental disorders, fecal incontinence, urinary incontinence, urinary tract infection (UTI), impaired intercourse, impaired fertility, and other abnormalities, such as limb anomalies, vertebral anomalies, neurologic deficits, and tracheoesophageal fistulas.

The history of imperforate anus management dates back to the seventh century, where the earliest reports of survival with surgery (rupture of an obstructing anal membrane) may be found. In 1835, Amussat performed a perineal proctoplasty. In the 1850s, various authors reported the use of colostomy, which opened the door for successful management of high ARM. An abdominal-perineal pull-through procedure was undertaken in the 1880s and advanced further by Rhoads.[3–5] In 1953, Stevens promoted a direct sacral approach to reconstruction, and in 1967, Kiesewetter combined these approaches into a two-stage sacroabdominoperineal pull-through procedure. Peña and Hendren ushered in the modern era of ARMs as well as cloacal management. Peña performed the posterior sagittal approach for the treatment of these malformations initially in 1980 and reported the results soon thereafter.[6]

Surgeons recognized the frequent association of urologic abnormalities associated with ARMs.[7–11] Similar recognition of the high incidence of spinal cord abnormalities, including occult spinal dysraphisms such as tethered cord, lipomas, neurenteric cysts, and diastematomyelia, advanced the management of these patients.[12–15] Patients with ARMs frequently require complex urinary reconstruction for which unique concerns must be addressed.[16]

DIAGNOSIS

Prenatal diagnosis of anorectal and urogenital malformations occurs with a frequency that ranges from 0% to 15.9% of screened cases.[17–19] It tends to be more commonly diagnosed in the more complex defects, such as cloaca and cloacal exstrophy. The advantages of having a prenatal diagnosis of these defects include planning for the delivery at a tertiary center that is familiar with the neonatal management of these types of anomalies, and preparing the parents for the birth of a child with serious congenital anomalies. Prenatal findings that should make the physician suspect an anorectal and urogenital malformation include distended distal bowel with or without intraluminal calcifications, in combination with urological abnormal findings (hydronephrosis or absent kidney) and/or vertebral anomalies.[20] Approximately 30% of the patients with cloacas have hydrocolpos, which can be seen in utero as a cystic pelvic mass of the fetus. Therefore, prenatal findings that suggest the presence of a cloacal anomaly include cystic pelvic masses and a combination of gastrointestinal and urological abnormalities. It is important to remember that 60% of patients with cloaca have duplications of the Mullerian structures; therefore, the finding of three cystic pelvic masses (bladder anterior and two hemivaginas with hydrocolpos posterior) represents a classic image of a CM.[20,21] Prenatal findings in cases of cloacal exstrophy include the nonvisualization of the bladder, a large midline anterior wall defect with an omphalocele, lumbosacral anomalies, and an elephant trunk–like image, representing the prolapsed ileum in between both hemibladders.[22,23]

CLASSIFICATION

The following proposed classification is anatomically descriptive and has therapeutic and prognostic implications. The defects are listed from the most benign to the most complex types. Interestingly, urologic anomalies, as well as digestive and skeletal ones, occur with

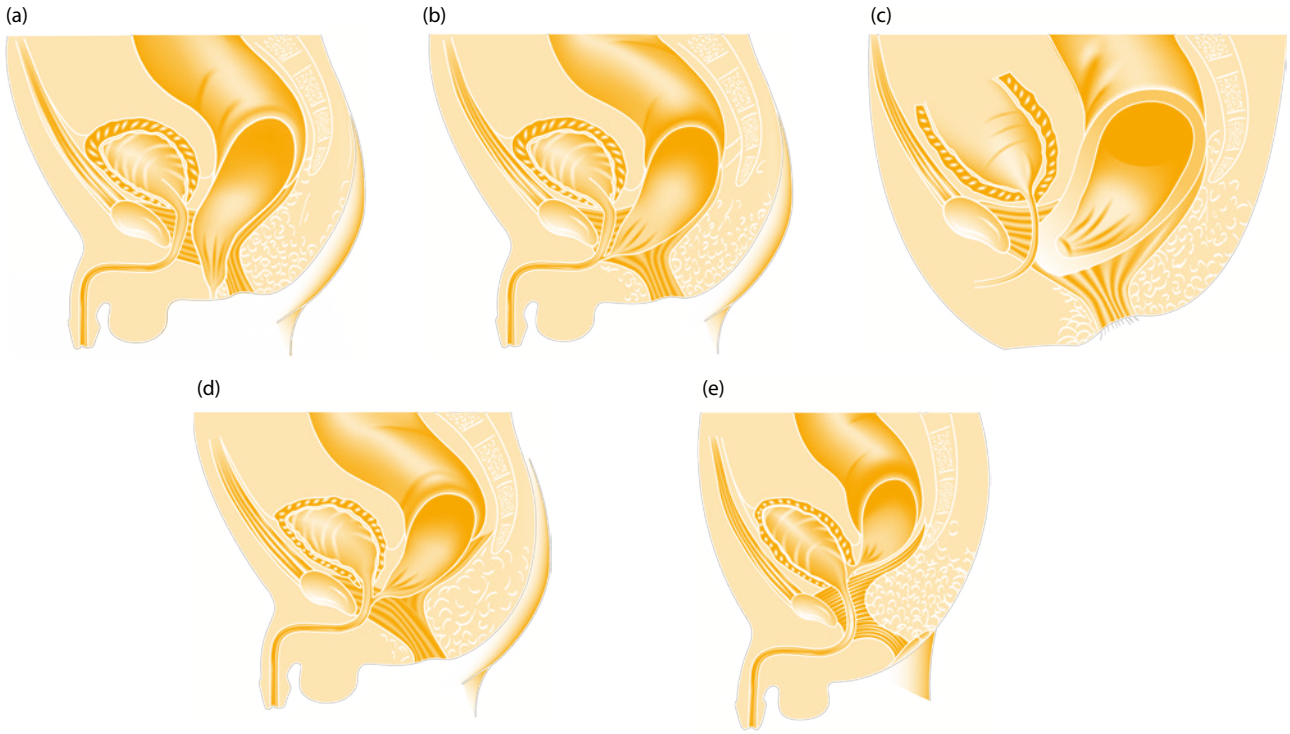

FIGURE 71.1 Diagrams of male ARM. (a) Rectoperineal fistula. (b) Rectourethral bulbar fistula. (c) Imperforate anus without fistula. (d) Rectourethral prostatic fistula. (e) Rectobladder neck fistula.

increasing frequency, almost in a linear fashion; the frequency increases the more complex the ARM.

1. Male types of ARMs (Figure 71.1)
   a. Rectoperineal fistula
   b. Rectourethral bulbar fistula
   c. Imperforate anus without fistula
   d. Rectourethral prostatic fistula
   e. Rectobladder neck fistula
   f. Cloacal exstrophy
   g. Complex anomalies
2. Female types of ARMs (Figure 71.2)
   a. Rectoperineal fistula
   b. Rectovestibular fistula
   c. Imperforate anus without fistula
   d. Cloaca with common channel <3 cm in length
   e. Cloaca with common channel >3 cm in length
   f. Cloacal exstrophy
   g. Complex anomalies

ASSOCIATED SYNDROMES

We now know that urinary, genital, and anorectal development are intimately interconnected. As early as 1829, Mayer recognized an association between vaginal agenesis and other congenital anomalies.[24] Kuster and Rokitansky independently confirmed this observation.[25,26] Hauser and Schreiner, in 1961, emphasized the association of vaginal agenesis with skeletal and renal anomalies.[27] Thus, the final association became known as the Mayer–Rokitansky–Kuster–Hauser syndrome. Upper tract anomalies are encountered in approximately one-third of these patients, mostly consisting of renal agenesis, renal ectopia, and renal fusion anomalies.[28,29] Frequent skeletal anomalies were also noted, many of which involved abnormal cervical and thoracic somite development. Duncan, in 1975, referred to this as the MURCS association: Mullerian duct aplasia, renal aplasia, and cervicothoracic somite association.[30]

Similar to those observations associated with vaginal agenesis, repetitive patterns of anomalies were seen with anorectal anomalies. This constellation originally became known as the VATER association: vertebral, anorectal, tracheoesophageal, and radial. Later, it was expanded to the VACTERL association: vertebral, anorectal, cardiac, tracheoesophageal, radial or renal, and limb.[31–33]

ASSOCIATED SACRAL AND VERTEBRAL ANOMALIES

Two important anomalies that have a demonstrated influence on the functional prognosis of patients with anorectal and urogenital malformations are those of the sacrum and the presence or absence of tethered cord. These two defects can be evaluated during the first few days of life; this will allow the doctor to establish the future quality of life of the patient. A patient with a poor sacrum and tethered cord has little chance of having normal bowel and urinary control. In addition, those patients must be followed on a long-term basis since they have a tendency to suffer renal injury.

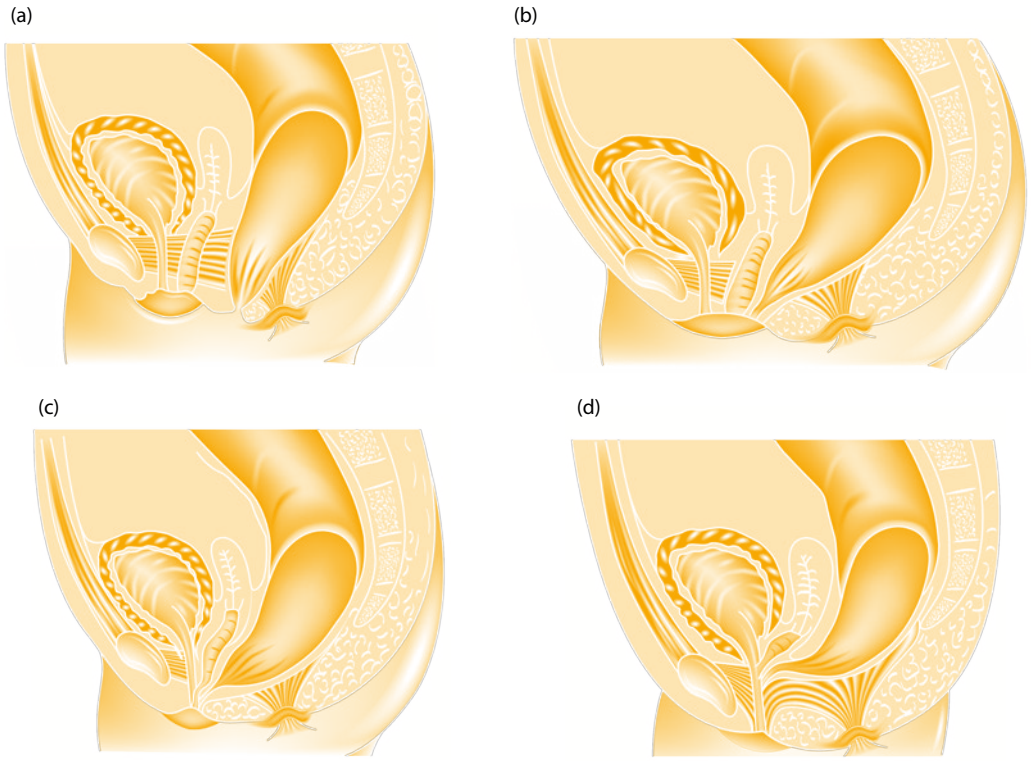

FIGURE 71.2 Diagrams of females with ARM. (a) Rectoperineal fistula. (b) Rectovestibular fistula. (c) Cloaca with a common channel length of <3 cm. (d) Cloaca with a common channel length of >3 cm.

The absence or presence of tethered cord seems to have more influence in the urinary tract. A deficient sacrum affects both urinary and bowel function, but it seems to have a major effect on bowel function. The sacral ratio is a valuable prognostic tool (Figure 71.3) because it quantifies the degree of sacral hypodevelopment. Patients with ratios of less than 0.4 are generally incontinent of stool. A sacral ratio of >0.7 predicts a good prognosis for bowel control. A sacral defect, particularly hemisacrum, in association with imperforate anus and a presacral mass is known as Currarino's triad; it has a strong familial tendency, and it is usually correlated with poor functional prognosis.[34,35] The types of ARMs more often associated with sacral defect and presacral mass are perineal fistula, vestibular fistula, and anorectal stenosis or atresia.

Lumbosacral anomalies, such as hemivertebrae, scoliosis, butterfly vertebrae, and hemisacrum, are common. The most frequent spinal cord problem is known as tethered cord,[14,36,37] but spinal lipomas, syringomyelia, and myelomeningocele are also commonly seen. The more complex the anorectal anomaly, the more likely the presence of associated spinal and vertebral anomalies. These problems are found by ultrasound or magnetic resonance imaging in a third to half of patients with ARMs.[13,38–40] It is still unclear how many of these lesions are clinically significant and which lesions require prophylactic surgery.[36,41]

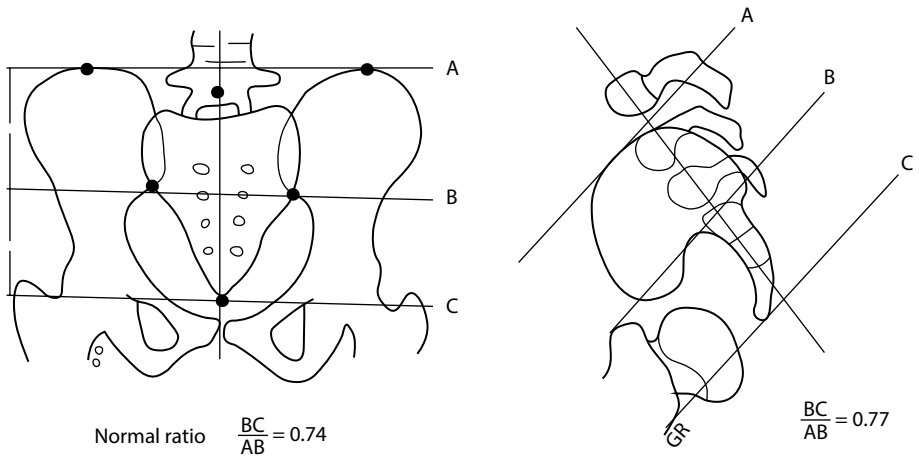

FIGURE 71.3 How to calculate the sacral ratio on AP and lateral sacral radiographs.

ASSOCIATED UROLOGICAL ANOMALIES

The prevalence of structural anomalies of the urinary tract in patients with anorectal anomalies is not insignificant. A review of a large ARM database from the senior author reveals the following urologic anomalies.[42] The most common urologic malformation associated with an ARM is an absent or multicystic kidney. The second most common defect is hydronephrosis. Another common urologic structural abnormality is vesicoureteral reflux (VUR), which was present in 290 out of 1370 female (21%) and 186 out of 1112 male (17%) patients in our ARM database. The presence of hydronephrosis and megaureter in a patient with ARM strongly suggests high-grade VUR, since the presence of a primary ureterovesical obstruction is uncommon in this population. There is one particular group of male patients born with the highest type of all defects (rectobladder neck fistula) who are born with a single kidney, hydronephrosis, and megaureter. We have seen this in 25 out of 111 (23%) patients born with that specific malformation. This particular group must be carefully followed since they tend to deteriorate and may progress to end-stage renal disease (ESRD), particularly if they have an abnormal sacrum and tethered cord. Some male babies are born with a narrowing or tortuosity in the proximal urethra. This is typically located at the fistula site where the rectum joins the urethra. We have seen this in 18 out of 1112 (2%) male patients. It can be helpful to repair this defect during the posterior sagittal anorectoplasty (PSARP), taking advantage of the excellent exposure provided by this approach. Approximately 10% of all male patients born with ARM have a bifid scrotum that can be mild or severe and associated with a penoscrotal transposition. The presence of a bifid scrotum can suggest a serious type of ARM (rectobladder neck or rectoprostatic fistula). Hypospadias can be present in approximately 8% of all male patients. Ectopic ureters occur in approximately 2% of patients with ARM, and the ureters tend to be connected close to or at the bladder neck level. They can occasionally be connected to the posterior urethra. In female patients, the ectopic ureter can be connected to the urethra or to the vagina. An ectopic vas deferens can be present in patients with ARM. An intraoperative vasogram has been used to document the connection to the bladder and/or ureter. These patients can develop recurrent orchioepididymitis. Epididymitis may reflect UTIs in the presence of dysfunctional voiding or urethral stricture pathology, or may be associated with intermittent catheterization. Congenital neurogenic bladder is present in babies born with a very deficient sacrum (sacral ratio <0.4), hemisacrum, and tethered cord. Neurogenic bladder in patients with normal lumbosacral spinal cord without cord tethering can be iatrogenic, secondary to a poor surgical technique observed during the repair of the ARM.[43] In addition to all the conditions mentioned above, the pediatric urologist will be consulted to take care of patients suffering from the sequelae of catastrophic operative complications. These include acquired urethral atresia, acquired urethral stricture, recurrent rectourethral fistula, and acquired rectourethral fistula. With the advent and popularization of the laparoscopic approach for the treatment of ARMs, a "posterior urethral diverticulum" has been described that actually represents a piece of rectum left attached to the urethra (usually in cases of rectourethral bulbar fistula).[44] That is one of the reasons we believe that the laparoscopic approach is appropriate in cases of rectobladder neck and some rectoprostatic fistulas. However, in cases of rectourethral bulbar fistula, it is difficult to reach the bulbar urethra and expose the distal extent of the fistula. This results in an amputation of the rectum, leaving a distal portion attached to the urethra. These patients characteristically pass large amounts of mucous through the urethra and dribble urine from the posterior urethral diverticulum in between voiding episodes.

Hyperchloremic metabolic acidosis is another potential problem for these children.[45,46] This condition results from urine passing from the bladder through a rectovesical or rectourethral fistula into the defunctionalized distal limb of colon following initial diverting colostomy. The resultant absorption of urinary constituents by the bowel results in the metabolic abnormality. The occurrence of this complication requires the presence of a urorectal fistula. A long segment of defunctionalized colon (large absorptive surface) that communicates with the fistula worsens the metabolic imbalance. Distal urinary obstruction, which may be structural (stricture) or functional (neurovesical dysfunction), also worsens this risk. UTI and renal insufficiency may also make this metabolic abnormality more likely. Creation of a low, fully diverting colostomy and ensuring effective bladder drainage help to avoid hyperchloremic metabolic acidosis. Once established, hyperchloremic metabolic acidosis is treated by the administration of oral alkalinizing agents, intermittent catheterization, vesicostomy, or early anorectal reconstruction with division of the fistula, depending on the clinical setting.

ASSOCIATED GYNECOLOGICAL ANOMALIES

The two most common gynecological anomalies are duplication of Mullerian structures, which happens in 34% of female patients with ARM, and absent vagina, which happens in 5.6% of patients with ARM.[47,48] Duplication of the Mullerian structures can be suspected when a vaginal septum is identified during the physical exam or during endoscopy in cases of cloaca. The vaginal septum is associated with two hemivaginas and two hemiuterii. In patients with cloaca, when a duplication of Mullerian structures is detected, we recommend testing the patency of both Mullerian structures by injecting saline solution through a 3 Fr feeding tube inserted into the fallopian tube on each side and confirming its patency by watching the fluid coming through the vagina. This maneuver can be done during the colostomy closure in patients with cloaca in which the abdomen was not entered during the main repair (cloacas with a common channel length shorter than 3 cm) or during the main repair when a laparotomy is needed (cloacas with a common channel length longer than 3 cm). With this maneuver, we hope to avoid patients with undetected

atretic Mullerian structures that can manifest during puberty as an acute abdomen from retained menstruation or blood in the abdominal cavity.[49] It is also important to make patients and parents aware when a duplication of Mullerian structures is detected due to its future obstetric implications (tendency for miscarriage and premature delivery). The incidence of duplicated Mullerian structures increases as the complexity of the malformation increases: perineal fistula 3%, vestibular fistula 6%, and cloaca 60%. A vestibular fistula with an absent vagina seems to be more frequent than previously thought, and was found in approximately 10% of the rectovestibular cases in our series.[48] The importance of early detection relies on the fact that the posterior sagittal approach offers an excellent opportunity for the vaginal reconstruction. An absent vagina occurs in perineal fistulas in 1% and in cloacas in 3.5%.

TREATMENT

Newborn Management

The decision-making algorithm during the initial management of male and female patients born with an ARM can be seen in Figures 71.4 and 71.5. A thorough perineal physical examination is the first step, which usually provides the most important clues about the type of malformation present. It is important not to make a decision about a colostomy or a primary surgery before 20–24 hours of age. The reason for waiting is that a significant intraluminal bowel pressure is required in order for the meconium to be forced through a fistula, overcoming the natural tone of the muscle complex that surrounds the rectum (Figure 71.6). The presence of meconium in the perineum represents evidence of a rectoperineal fistula or a rectovestibular fistula. A perineal fistula in females is easily seen (Figure 71.7); a vestibular fistula, on the other hand, must be searched for, immediately outside the hymen, and sometimes it is not easy to identify (Figure 71.8).

The presence of meconium in the urine in a male patient establishes the diagnosis of a rectourinary fistula. The presence of a single perineal orifice in a female newborn makes the diagnosis of a cloaca. Radiologic evaluations do not show the true anatomy before 24 hours because the rectum is collapsed and compressed by the muscle tone of the sphincters that surround its lower part (Figure 71.6). Therefore, radiologic evaluations done too early (before 24 hours) most likely will reveal a false image of a "very high rectum."

During the first 24 hours, the newborn should receive intravenous fluids, broad-spectrum antibiotics, and nasogastric decompression to prevent aspiration of gastric content. The clinician should use these hours to rule out the presence of associated defects, such as cardiac malformations, esophageal atresia, and urologic problems. An echocardiogram can be performed, and the baby should be checked for the presence of esophageal atresia. A plain anterior-posterior (AP) and lateral radiographs of the lumbar spine and sacrum should be taken to evaluate for hemivertebrae and sacral anomalies. A spinal ultrasound helps to screen for tethered cord. Ultrasonography of the abdomen will detect the presence of hydronephrosis, and a pelvic ultrasonography in females with cloaca evaluates for the presence of hydrocolpos.

A pediatric urologist should be involved in the initial management of a newborn with an ARM. The baby should not be taken to the operating room to create a colostomy or to receive an anoplasty without being evaluated for important urological problems, mainly hydronephrosis. At the minimum, a renal and bladder ultrasound should be performed. A spinal ultrasound should also be included in the initial evaluation. A voiding cystourethrogram will

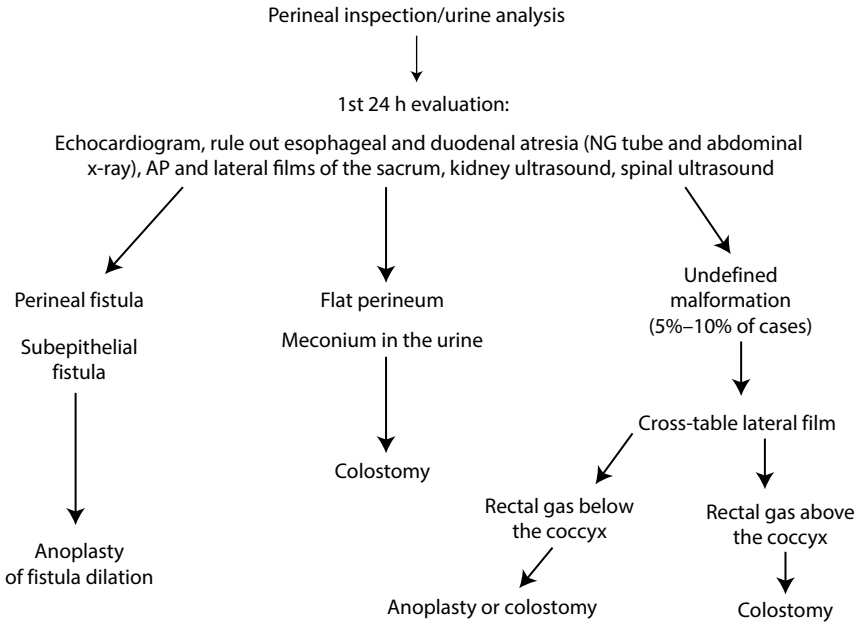

FIGURE 71.4 Decision-making algorithm for newborn males with ARM.

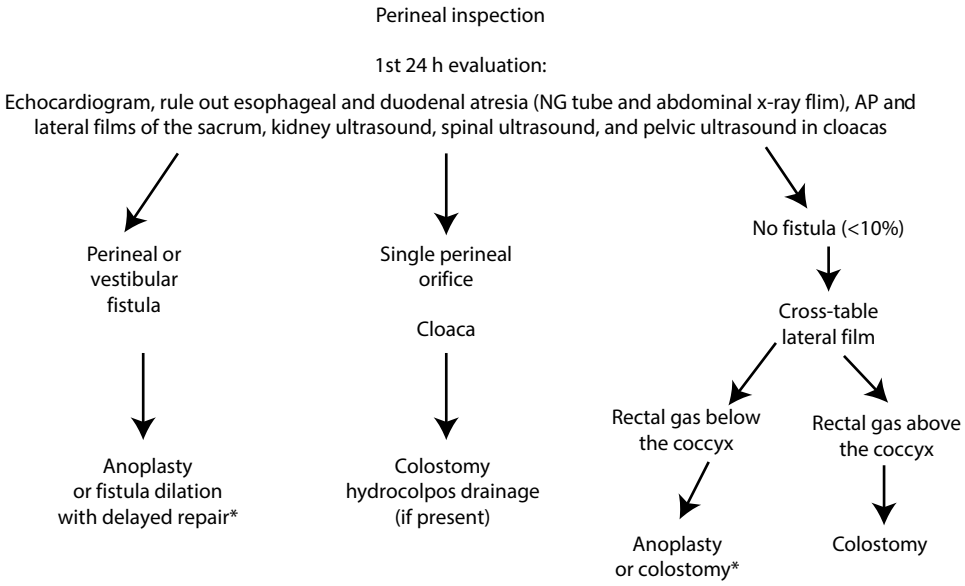

FIGURE 71.5 Decision-making algorithm for newborn females with ARM.

FIGURE 71.6 Normal anatomy in a male patient, showing the funnel-shaped muscle complex.

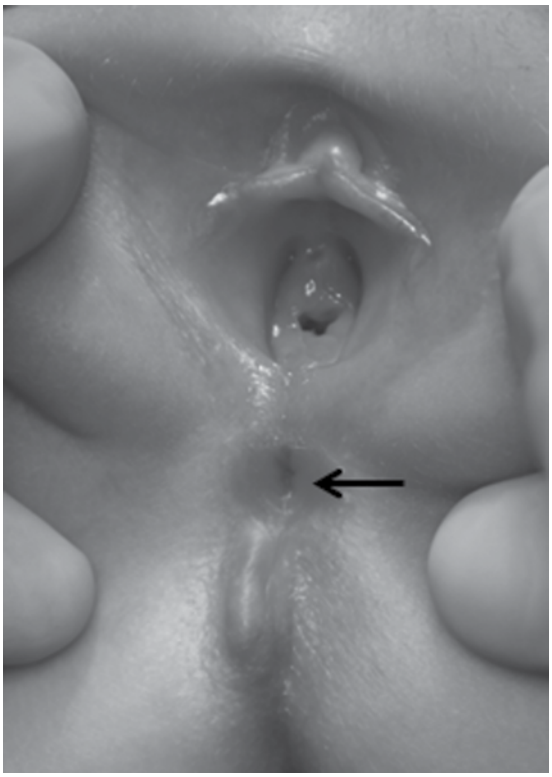

FIGURE 71.7 Female patient with a rectoperineal fistula (arrow).

ultimately be needed, but its interpretation with an intact fistula can be somewhat difficult, and so it may be deferred until after the primary operative intervention.

A significantly abnormal sacrum (sacral ratio of less than 0.4) and/or the presence of a tethered cord increases the risk of developing a neurogenic bladder, even if the initial ultrasound does not demonstrate hydronephrosis. A long common channel (>3 cm) in cloacal patients is also a risk factor for neuropathic voiding dysfunction.[42] Some patients with normal upper urinary tracts develop nephropathy as time goes by, especially when they have an abnormal sacrum and/or tethered cord. Careful urologic follow-up is mandatory in those patients deemed at high risk for neuropathic involvement to avoid irreversible renal injury.

At the time of colostomy creation in cloaca patients, it is mandatory to drain any hydrocolpos, if present. The hydrocolpos can compress the trigone of the bladder and may produce an extrinsic ureterovesical obstruction.

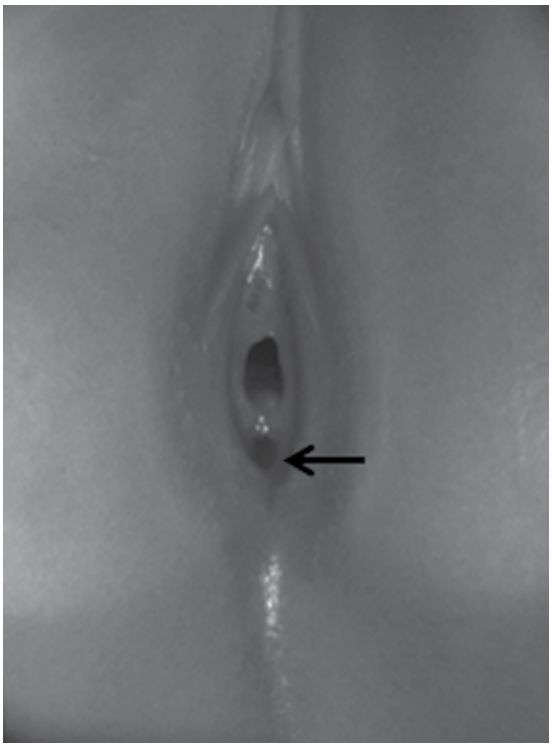

FIGURE 71.8 Female patient with a rectovestibular fistula (arrow).

This can result in secondary hydroureteronephrosis. If left undrained, there is also the risk of pyocolpos and even perforation. If the hydrocolpos is not large enough to reach the abdominal wall above the bladder, to be matured to the skin as a stoma, it can be drained with a transabdominal pigtail drain. Because a significant number of these patients have two hemivaginas, the surgeon must be certain that the tube inserted into the hydrocolpos is draining both hemivaginas. Occasionally, one has to open a window in the vaginal septum to drain both with a single tube. The hydrocolpos should be drained permanently until the main cloacal repair. Many patients are subjected to unnecessary vesicostomies, ureterostomies, and nephrostomies to alleviate the obstructive uropathy. In many cases, the simple drainage of the hydrocolpos allows for the decompression of the ureters and renal pelvis. We specifically suggest draining the hydrocolpos first, and then, after 48 hours, reevaluate the magnitude of the hydronephrosis and ureteral dilation. Interestingly, in many cases the drainage of the hydrocolpos will allow for better drainage of the ureters and will facilitate more efficient bladder emptying.

If the baby has signs of a perineal or vestibular fistula, an anoplasty can be performed without a protective colostomy in the newborn period. If the baby is clinically unstable from associated abnormalities or is extremely premature, or if the clinician chooses to wait until the baby is a little older, the fistula can be gently dilated. The repair in such cases should not be delayed more than several months.

After 24 hours, if no meconium is seen on the perineum or in the urine, a cross-table lateral x-ray film with the baby in prone position (Figure 71.9) should be obtained. If the gas in the rectum is located below the coccyx and the baby is in stable condition with no significant associated defects, depending on the surgeon's experience, a posterior sagittal operation without a protective colostomy can be considered. A more traditional, conservative alternative would be to perform a colostomy, with the definitive repair planned for a second stage. If rectal gas is seen above the coccyx or the patient has meconium in the urine, a single perineal orifice (cloaca), significant associated defects, and/or an abnormal sacrum or a "flat bottom," a colostomy is recommended with postponement of the main repair for a subsequent operation. This can be performed 2–3 months later after a distal colostogram delineating the anatomy is performed, provided that the baby is gaining weight normally. Antibiotic chemoprophylaxis is indicated to prevent urinary tract infectioun complications, particularly if VUR is present. Performing the definitive repair at 2–3 months of age has important advantages for the patient, including less time with an abdominal stoma, less size discrepancy between the proximal and distal bowel at the time of colostomy closure, easier anal dilation, and no recognizable psychological sequelae from painful perineal maneuvers. In addition, at least theoretically, placing the rectum in the right location early in life may provide an advantage in terms of the potential for acquired local sensation. The potential advantages of an early operation must be weighed against the possible disadvantages of an inexperienced surgeon unfamiliar with the minute anatomic structures of an infant's pelvis. A trend to repair these defects without a protective colostomy[50–52] must be balanced against the concern that such a repair without a colostomy is done without precise anatomic information about the patient's specific type of anorectal defect. The most catastrophic complications seen in patients operated on without a colostomy occurred in patients in whom the surgeon did not have a properly done preoperative distal colostogram. While looking for the rectum, the surgeon might inadvertently find and injure the urethra, an ectopic ureter, the bladder neck, the vas deferens, or the seminal vesicles.[43]

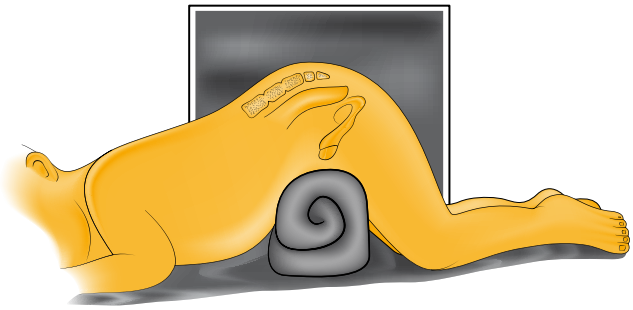

FIGURE 71.9 Cross-table lateral x-ray film with the baby in prone position.

Newborn Unified Management for Cloacal Exstrophy

When a patient is born with cloacal exstrophy, we strongly recommend a unified neonatal approach that should involve

a pediatric surgeon, a pediatric urologist, a pediatric gynecologist, an orthopedic surgeon, and a neurosurgeon in order to give the patient the best possible functional and anatomical outcome.[53] During the initial intervention, it is critical to ensure that the entire gastrointestinal tract is incorporated into the fecal stream, creating a real end colostomy. The most common error in the early management of these patients is the creation of an ileostomy, leaving the colon attached to the urinary tract. This allows the urine to be absorbed in the colon, provoking hyperchloremic acidosis, as described above. During the first operation, surgeons must refrain from using gastrointestinal tissue to reconstruct the urogenital tract since the future possibility of the patient having a bowel pull-through depends on the presence of enough colon to form solid stool.[54] The decision to use colon, small bowel, or stomach to reconstruct the urinary tract must be made much later in life, after the decision between a pull-through or permanent stoma has been made. The omphalocele should be closed, if possible, during the initial procedure. The Mullerian structures in females must be inspected, and the two hemibladders must be approximated and sutured together in the midline for a later urological reconstruction.

Colostomy

The recommended colostomy in patients with ARM is created in the descending colon with separated stomas (Figure 71.10), to ensure that a complete diversion is performed in order to avoid fecal contamination of the urinary tract. It is important to leave the entire loop of sigmoid colon distal to the colostomy to allow the rectal pull-through. The colostomy is fashioned by making an oblique left lower quadrant incision. The colon is divided, with the bowel openings placed at opposite ends of the wound. The proximal stoma is located just after the colon comes off its left retroperitoneal attachment. The distal stoma is created in the upper sigmoid, and is made intentionally small in an attempt to prevent prolapse. The distal segment should be copiously irrigated to remove all meconium. The mucous fistula should be placed far enough away from the functional stoma, leaving enough space for a stoma bag to cover only the proximal stoma. This way, no stool spillage downstream can occur, and the stoma bag stays on more easily. Significant morbidity is associated when a colostomy is not properly done.[55]

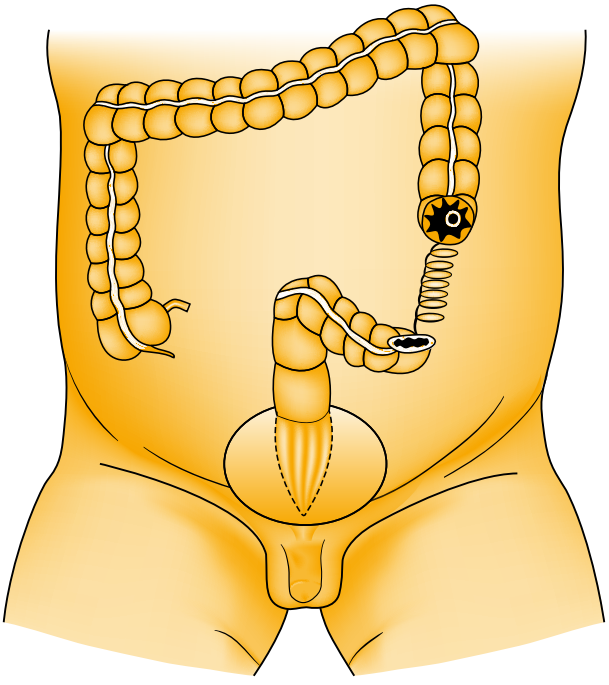

FIGURE 71.10 Descending colostomy with separated stomas.

It is a relatively frequent event for a pediatric urologist to be called in consultation to see a baby with an ARM with a colostomy, suffering from frequent episodes of urosepsis. The urologist must first look at the colostomy, to rule out fecal contamination of the urinary tract due to a defective colostomy. Transverse colostomies have serious disadvantages, which include prolapse, difficult cleaning of the distal segment, and difficult and risky delineation of the downstream rectourinary anatomy during the distal colostogram. Such colostomies also lead to megarectosigmoid and a left microcolon in the defunctionalized segment, particularly when the colostomy is left in place for many months. A colostomy that is placed too low in the sigmoid can interfere with the pull-through. A loop colostomy leads to distal contamination of the urinary stream if there is a fistula and to a dilated megarectosigmoid from stool spillage.

High-Pressure Distal Colostogram

Before the definitive repair, the most valuable radiologic study to be performed is the "high-pressure distal colostogram" to define the precise location of the fistula in male patients. In fact, the risk of urologic injuries seems to increase when patients undergo repair without this study.[43] Water-soluble contrast medium is instilled into the distal stoma, which fills the distal intestine and enables demonstration of the location of the blind rectum, the precise site of a rectourinary fistula, the relationship with the sacrum, and the amount of distal colon available for the pull-through. Since the rectum is surrounded by striated muscle, upon injection of the contrast, the distal rectum remains collapsed and prevents filling of the most distal part, giving the false impression that we are dealing with a "high defect," and it may also prevent demonstration of a rectourinary fistula, which is always located at the most distal part of the rectum. To avoid this problem, the contrast material must be injected with considerable hydrostatic pressure under fluoroscopic control, to overcome the muscle tone. The use of a Foley catheter is recommended; it is passed through the distal stoma, the balloon is inflated (2–5 mL), and it is pulled back as far as possible to occlude the stoma during the injection of the contrast medium. All this is done under fluoroscopic control. The first images are obtained in an anterior posterior position, and they allow the surgeon to determine the length of bowel distal to the colostomy that is available for the pull-through. The patient is then placed in perfect lateral position, and the high-pressure injection of contrast must continue until the contrast passes through the fistula into the urinary tract. In cases of rectourethral fistula

(prostatic and bulbar), with this study, the surgeon knows precisely where to find the rectum. In cases of rectobladder neck fistulas, the surgeon does not expect to find the rectum through the posterior sagittal approach and so avoids a blind perineal dissection. In this latter case, the surgeon can prepare the patient for an additional laparoscopy or laparotomy to mobilize a very high rectum.

PSARP for Rectoperineal Fistula in Males and Females and for Rectovestibular Fistula (Figure 71.11)

The repair of these defects consists of a small anoplasty with minimal mobilization of the rectum, sufficient for it to be transposed and placed within the limits of the sphincter. This is a meticulous operation and can be done during the neonatal period without a colostomy. The most common complication during the repair of this defect is a urethral injury in male patients, which can be avoided by placing a urethral catheter and taking particular care during the dissection of the anterior rectal wall. In female patients, a vaginal injury may occur, and it can be avoided by meticulous dissection and constant checking of the vagina and rectal wall's thickness with the usage of a lacrimal duct probe. Special emphasis should be placed on this dissection in cases of rectovestibular fistula in which there is a very thin common wall between the rectum and vagina. These patients, both boys and girls, have an excellent functional prognosis for bowel and urinary control, provided they have a normal sacrum and no tethered cord, and receive a good operation. These patients only have problems with bowel control if they are subjected to an inadequate surgical technique; if they are not treated adequately to prevent constipation, fecal impaction, and overflow pseudoincontinence; and if they have significant associated spinal or sacral problems.

PSARP for Rectourethral Bulbar and Prostatic Fistula and Imperforate Anus without Fistula (Figure 71.12)

A Foley catheter is inserted through the urethra. In about 5% of cases, this catheter goes into the rectum rather than into the bladder. To avoid this, the catheter must be intentionally directed anteriorly by the use of a curved lacrimal duct probe inserted in the distal tip of the catheter or using a coude catheter to find its correct path. When these maneuvers fail to pass the catheter into the bladder, the catheter can be placed through a wire introduced through the cystoscope. Occasionally, the catheter must be positioned intraoperatively under direct vision once the fistula is visualized. The patient is placed in prone position with the pelvis elevated. A posterior sagittal incision is used. The skin is opened using a very fine-needle cautery, and the parasagittal fibers and muscle complex are divided exactly in the midline. The fibers of the muscle complex run

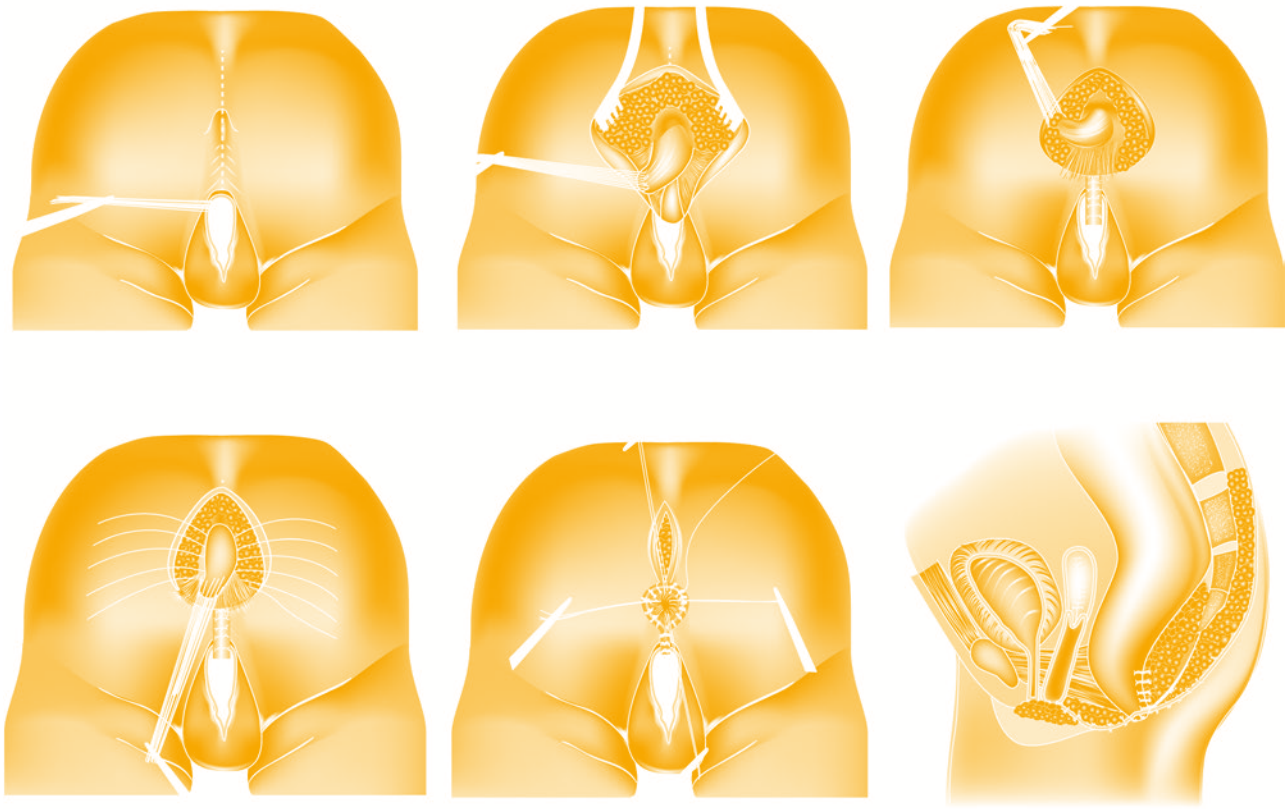

FIGURE 71.11 Diagram showing the surgical repair in the case of a rectovestibular fistula.

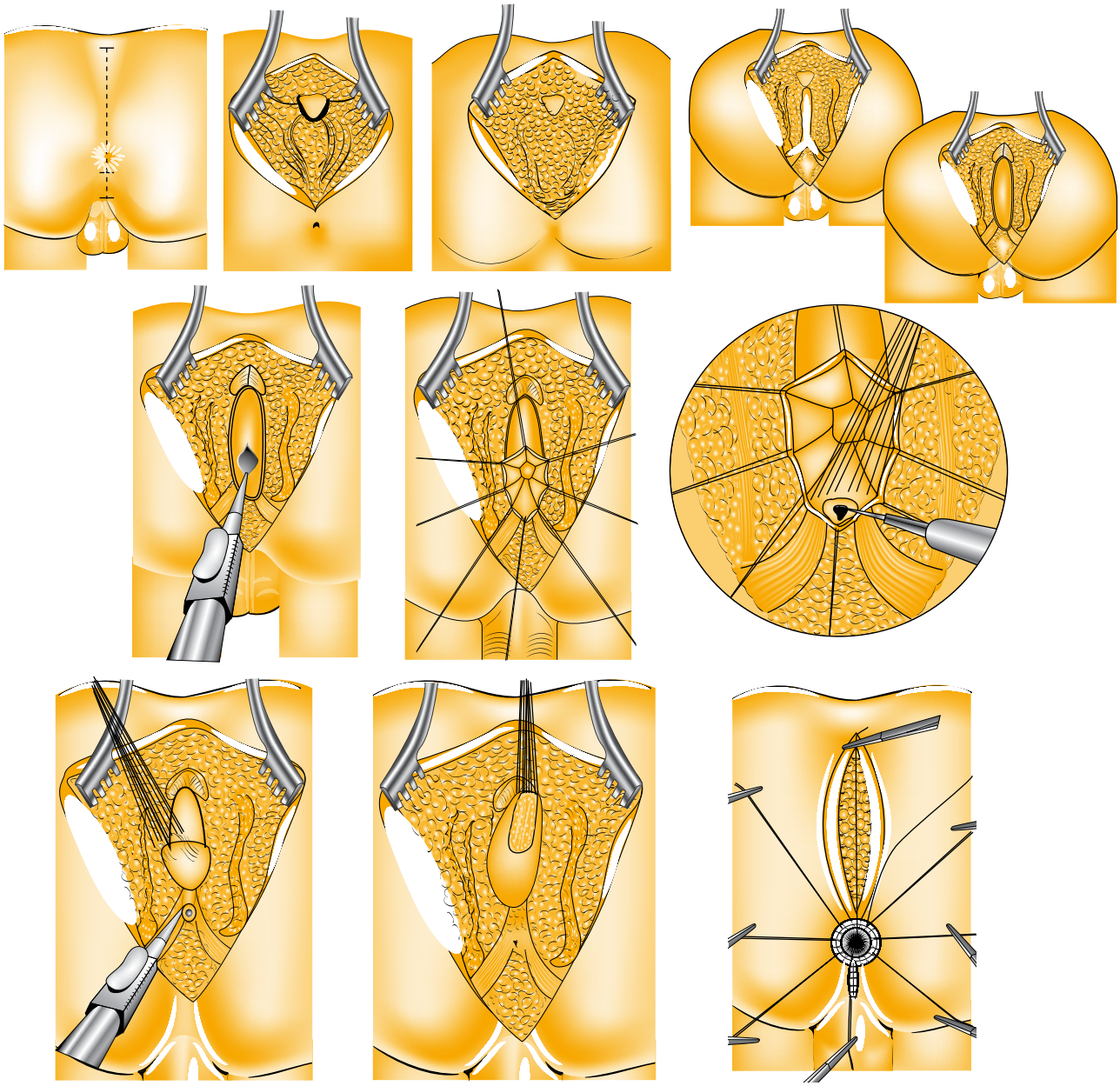

FIGURE 71.12 Diagram showing the surgical repair in the case of a rectourethral bulbar fistula.

perpendicular and medial to the parasagittal fibers. The crossing of the muscle complex fibers with the parasagittal fibers represents the anterior and posterior limits of the new anus. These limits can be seen most clearly with the use of an electrical stimulator. The levator muscle, which lies deep in the incision, is then divided in the midline. The higher the malformation, the deeper the levator muscle is found. The levator muscle fibers run parallel to the skin incision. Levator muscle and muscle complex are in continuum. When all muscle structures have been divided, the rectum can be seen. In cases of rectourethral bulbar fistulas, the distal rectum is prominent, and it almost bulges into the wound. In cases of rectoprostatic fistulas, the rectum is located much higher, just under the coccyx, and is not as prominent. In cases of rectobladder neck fistulas, the rectum is not visible through this approach, and searching for it risks injuring other structures.

Two silk sutures are placed in the posterior rectal wall on both sides of the midline. The rectum is opened between the sutures, and the incision is continued distally, exactly in the midline, down to the fistula site. Temporary silk sutures are placed on the edges of the open posterior rectal wall for traction. One silk stitch is placed inside of the fistula, and it will serve as a guide to locate the fistula site after the rectum is completely separated from the urinary tract. In patients with imperforate anus without fistula, the rectum is usually located at the level of the bulbar urethra, and even though there is no fistula connection, the common wall with the urethra is the same as in a case of a rectourethral bulbar fistula. The anterior rectal wall

immediately above the fistula is a thin structure. There is no plane of separation between the rectum and urethra in that area. A plane of separation must be created in the common wall. Multiple 6-0 silk sutures are placed through the rectal mucosa immediately above the fistula in a semicircle. The rectum is then separated from the urethra, creating a submucosal plane for approximately 5–10 mm above the fistula site. During this delicate dissection, it is very helpful to dissect the rectum laterally, very close to the rectal wall, until both dissections (lateral and medial) meet, separating the rectum completely from the urinary tract. The separation of the rectum from the urinary tract is the most delicate part of the operation, and it represents the main source of urologic catastrophic complications, including damage of the vas deferens, seminal vesicles, prostate, and bladder denervation, as well as damage to the nervi erigent. This is particularly common when these operations are performed without a distal colostogram and during the operation the surgeon is searching for the rectum. We have seen patients who suffered a complete section of the urethra, a pull-through of bladder, or an ectopic ureter.

Once the rectum is fully separated, a circumferential perirectal dissection is performed to gain enough rectal length to reach the perineum. The rectum is surrounded by a conspicuous whitish fascia. The dissection must be performed between this fascia and the rectal wall to avoid damage to the innervation of the bladder and genitalia. In cases of a fistula opening into the bulbar urethra, the dissection necessary to pull the rectum down to the perineum is minimal, whereas in cases of prostatic fistula, the perirectal dissection is considerable. In both cases, enough rectal length must be gained in order to perform a comfortable, tension-free anastomosis between the rectum and the skin. As traction is exerted on the mobilized rectum, some grooves can be seen in the rectal wall, which demonstrate the tension lines that hold the rectum. These indentations are nerves and vessels that must be divided.

Once the rectum has been fully mobilized, a decision must be made concerning the need for tailoring of the rectum. The size of the rectum can be evaluated and compared with the available space so that its size matches the limits of the sphincter. If necessary, the rectum can be tapered by removing part of the posterior wall, and reconstructed with two layers of interrupted, long-lasting, absorbable sutures. The tapering of the rectum must always be done on the posterior rectal wall. The rectum must be mobilized enough to guarantee that the part of the intestine that will be adjacent to the closed urethral fistula is normal rectal wall to avoid a recurrent rectourethral fistula. The anterior rectal wall is often damaged to some degree as a consequence of the separation between the rectum and urethra. To reinforce this wall, the smooth muscle layers can be sutured together with interrupted 5-0 absorbable suture. The urethral fistula is sutured with long-term, absorbable sutures. The rectum is placed in front of the levator muscle and within the limits of the muscle complex and external sphincter. The electrical stimulator is helpful in identifying the limits of these muscle structures. Anterior and posterior limits of the external sphincter are temporarily marked with silk sutures. In cases in which the incision is extended anteriorly beyond the limits of the sphincter, it is necessary to repair the anterior perineum with interrupted, long-term, absorbable sutures to bring together both anterior limits of the external sphincter. Long-term absorbable sutures are placed on the posterior edge of the levator muscle. The posterior limit of the muscle complex must also be reapproximated behind the rectum. These sutures should include part of the rectal wall in order to anchor it and help avoid rectal prolapse.

The anoplasty is performed with 16 interrupted, long-lasting, absorbable sutures. Anoplasty sutures are placed under slight tension, so that once cut, the anus retracts slightly. The wound is then closed, bringing together corresponding sphincteric structures in the midline. The Foley catheter is left in place for 7 days. The patient receives broad-spectrum antibiotics for 1 day and prophylactic antibiotics while the Foley is in place.

PSARP with Laparoscopy or Laparotomy for Rectobladder Neck Fistula

For the repair of rectobladder neck fistulas, the entire lower part of the patient's body, from the chest down, is included in the sterile field (total body preparation), so that the surgeon can work alternatively in the abdomen and the perineum (Figure 71.13). The abdomen is entered via either laparotomy or laparoscopically,[56] and the rectosigmoid colon is mobilized. The peritoneum should be divided

FIGURE 71.13 Total body preparation in order to have a sterile field from the nipple line down, including the back.

around the distal rectum to create a plane of dissection to be followed distally. The dissection must be conducted right on the rectal wall. At the point where the rectum becomes narrow, where it communicates with the bladder neck, it should be divided. The bladder side of the fistula should be sutured by laparotomy or ligated with an endoloop by laparoscopy. In this very high defect, the rectobladder neck fistula is located approximately 2 cm below the peritoneal reflection, and the rectum communicates with the urinary tract in a T fashion, which means that there is no common wall between the distal part of the rectum and the urinary tract. This anatomic fact makes the separation of the rectum from the bladder neck a much easier and safer maneuver. That is the reason why this separation can be done safely laparoscopically. The surgeon must be careful to avoid damage to the vas deferens, which runs very close to the bowel. With a laparoscopic technique, separation of the rectum from the bladder neck is straightforward. Gaining adequate length, particularly with a high rectum, is challenging, and must be meticulous so as to avoid devascularizing the distal rectum.

The next step consists of mobilizing enough rectum to reach the perineum without tension. As this is a very high defect, mobilization of the rectum requires special maneuvers. Ligation of the inferior mesenteric vessels as high as possible, very close to their origin near the aorta, would mobilize the rectum, but would probably compromise the blood supply of the rectum because the arcades that connect the middle colic vessels with the inferior mesenteric ones may have been interrupted at the time of the colostomy creation. Therefore, the surgeon must instead ligate the most distal branches of the inferior mesenteric vessels close to the rectum. If this is done, the more proximal branches of the inferior mesenteric vessels must be left intact to guarantee a good blood supply that runs intramurally to the rectum.

If it is necessary to gain extra length, a plastic operation of the distal dilated portion of the rectum can also be performed. A combination of these maneuvers usually allows the intestine to reach the perineum, provided the colostomy does not interfere with the pull-through of the rectum. This can be anticipated by the careful analysis of the distal colostogram images, which demonstrates the precise length of intestine available from the colostomy to the end of the rectum. If the colostomy was placed too distal in the sigmoid, the surgeon may have to take down the mucous fistula and leave it as a Hartman's pouch to allow for the pull-through. The rectum should be preserved and never discarded, as it performs a vital reservoir function. At this point with the legs lifted, a perineal midsagittal posterior incision is performed. The presacral space is dissected and visualized through the abdomen. The rectum is pulled through. Further laparoscopic or laparotomy dissection can be performed while pulling gently on the rectum. The rectum is tacked to the muscle complex, and an anoplasty is performed as described previously.

PSARVUP with or without Laparotomy for Cloacal Malformation

This female malformation is considered separately because of its complexity. The reconstruction requires a very delicate, meticulous technique (posterior sagittal anorecto-vagino-urethroplasty [PSARVUP]), as well as creativity, imagination, and a resourceful, experienced surgeon. Repair of this defect has three main goals: achievement of urinary control, bowel control, and sexual function. Because a spectrum of defects exist, these goals are achieved in some cases; in others, however, the defect is repaired anatomically but the patients are left with functional sequelae that require extensive medical assistance to provide a good quality of life. During the surgical exploration, the surgeon must be prepared to find bizarre anatomic arrangements of the rectum, vagina, and urinary tract.

Before undertaking the repair of a cloaca, the surgeon should perform an endoscopy with the specific purpose of determining the length of the common channel. A contrast study of each of the three systems is very valuable and can be ideally done with a three-dimensional rotational scan, injecting contrast material through the stoma and through the single perineal orifice.[57] The accompanying videos demonstrate the rotational scan in different malformations (Videos 71.1–71.5).

There are two well-characterized groups of patients with a cloaca. These two groups represent different technical challenges and must be recognized preoperatively. The first consists of patients with a common channel shorter than 3 cm. Fortunately, this group represents the majority. These patients can usually be repaired via a posterior sagittal approach alone, without laparotomy.

The second group consists of patients with longer common channels. These patients usually need laparotomy, followed by a decision-making process that usually requires intricate vaginal maneuvers or vaginal replacement, tricks to mobilize a high rectum, knowledge of bladder neck anatomy, and decision making related to ectopic ureters, if found. This group should be cared for at centers with special dedication to the repair of these defects.[58]

Cloacas with a Common Channel Shorter than 3 cm

The incision extends from the middle portion of the sacrum down to the single perineal orifice. The entire sphincter mechanism is divided in the midline. The first structure that the surgeon will find after division of the sphincter mechanism is usually the rectum. The rectum is opened in the midline, and silk stitches are placed along the edges of the posterior rectal wall. The incision is extended distally through the posterior wall of the common channel. The entire common channel is opened, and its lumen is exposed to allow confirmation of its length under direct vision. The rectum is then separated from the vagina. This is performed in the same way as for repair of a rectovestibular fistula because the rectum and vagina share the same common wall already described. In patients with a vaginal septum, the rectum must be searched for at the posterior aspect of this septum.

Once the rectum has been completely separated from the vagina, a maneuver called total urogenital mobilization is used.[59] Prior to this maneuver, the vagina was separated from the urinary tract, which was a technically challenging maneuver associated with significant morbidity.

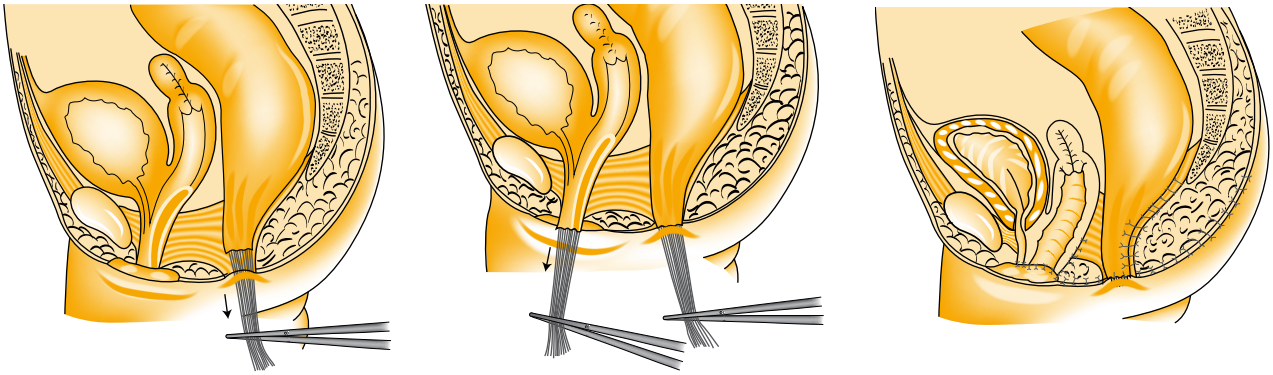

FIGURE 71.14 Total urogenital mobilization maneuver.

Total urogenital mobilization consists of mobilization of both the vagina and urethra as a unit without separating one from the other (Figure 71.14). After the rectum has been separated, multiple silk stitches are placed through the edges of the vagina and the common channel to apply uniform traction on the urogenital sinus. Another series of fine stitches are placed across the urogenital sinus approximately 5 mm proximal to the clitoris (Figure 71.15). The urogenital sinus is transected between the last row of silk stitches and the clitoris. Applying uniformed traction on the multiple sutures, the common channel (urogenital sinus) is separated from the pubis. The dissection takes advantage of the fact that there is a natural plane between it and the pubis. Very rapidly and in a bloodless field, one can reach the upper edge of the pubis. There, a fibrous, avascular structure that gives support to the vagina and bladder is identified.

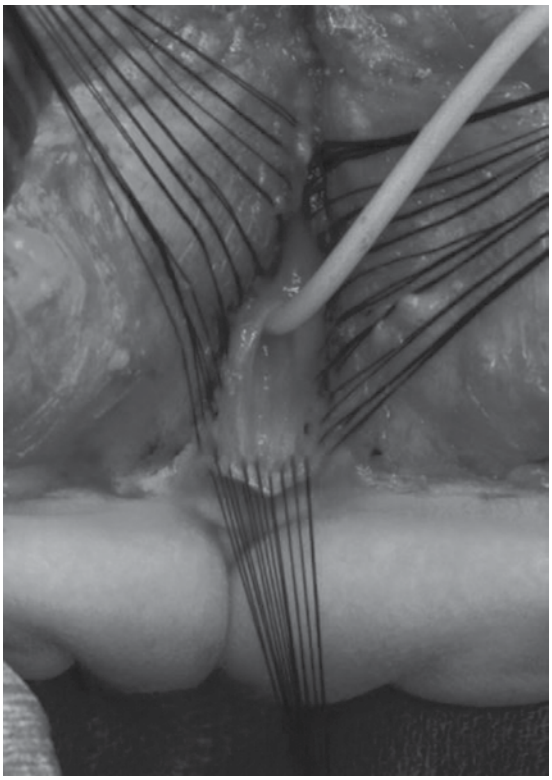

FIGURE 71.15 Silk stitches placed in the lateral walls of the common channel and behind the clitoris for the total urogenital mobilization.

This structure is called the suspensory ligament of the urethra and bladder. This ligament is divided, which immediately provides significant mobilization (between 2 and 3 cm) of the urogenital complex. One can then dissect the lateral and dorsal walls of the vagina to gain an extra 5–10 mm. This dissection is enough to repair about 60% of all cloacas and is a reproducible maneuver. It has the additional advantage of preserving an excellent blood supply to both the urethra and vagina. It places the urethral opening in a visible location and provides a smooth urethra that can easily be catheterized, if necessary. What used to be the common channel is divided in the midline to form two lateral flaps that are sutured to the skin to create the new labia. If a vaginal septum is present, it is resected. The vaginal edges are then mobilized to reach the skin to create the introitus. The limits of the sphincter are electrically determined. The perineal body is reconstructed by bringing together the anterior limit of the sphincter. The rectum is placed within the limits of the sphincter in the manner previously described. Patients can eat the same day, and the pain is usually easily controlled. Patients are discharged 48 hours after surgery. The Foley catheter is kept in place for at least 2 weeks.

Cloacas with a Common Channel Longer than 3 cm

When endoscopy and a cloacagram show that the patient has a long common channel, the surgeon must be prepared to face several significant technical challenges.

Patients with a long common channel should receive a total-body preparation because it is likely that laparotomy will be required. The rectum is separated from the vagina and urethra via a posterior sagittal incision, or via laparotomy when it is located very high. In cloacas with a common channel of 3–5 cm, the total urogenital mobilization is attempted. Occasionally, we have been able to repair one of these cases without opening the abdomen. However, in the majority of these cases it is necessary at this stage to open the abdomen to divide all the avascular attachments of the urethra and vagina. This extra dissection may be enough to complete the repair. If that is not the case, the vagina must be completely separated from the urinary tract. This represents the most technically

demanding maneuver in the repair of these defects. The bladder is opened in the midline, and feeding tubes are placed into the ureters to protect them. A long and wide common wall between the vagina and the trigone of the bladder exists, and both ureters run through this common wall. The ureters sometimes have to be skeletonized during this separation, and therefore require protection. The assistant places two fingers inside the bladder and holds traction to it so the separation between the urinary tract and vagina is initiated. This dissection is continued all the way down to meet the previous dissection initiated from below. The vagina is thus separated from the urinary tract, with care being taken to preserve its blood supply from the uterine vessels. Once the vagina has been separated from the bladder and urethra, the surgeon has to make a decision based on the specific anatomic findings. The vagina at this point may reach the perineum. If it does not reach the perineum by a few millimeters, at this stage the surgeon can carve the pubic bone cartilage and make the trajectory of the urethra and vagina shorter by making it straighter (normally, the urethra and vagina have to pass underneath the pubic bone in order to reach the perineum). If the vagina does not reach the perineum, a Heinecke–Mikulicz maneuver may be done, which seems to be useful to gain some minor vaginal length. After these maneuvers, if the vagina cannot be mobilized to the perineum, the next step includes considering a maneuver called vaginal switch, if the anatomy allows for it.

The patency of the Mullerian structures is investigated by passing a No. 3 feeding tube through the fimbriae of the fallopian tubes and injecting saline. If one of the systems is not patent, the atretic Mullerian structure should be excised, with great care taken to avoid damage to the blood supply of the ipsilateral ovary. When both Mullerian structures are atretic, they should be left in place. The patient must be monitored closely and further investigated with ultrasound when she enters puberty.

Vaginal Switch Maneuver

A specific group of patients are born with hydrocolpos and two hemivaginas. The hemivaginas are very large, and the two hemiuteri are very separated, the distance between them being longer than the vertical length of both hemivaginas. In these cases, it is possible to perform a maneuver called a vaginal switch.[60] One of the hemiuteri and the ipsilateral fallopian tube are resected, with particular care taken to preserve the blood supply of the ovary. The blood supply of the hemivagina of that particular side is sacrificed. The blood supply of the contralateral hemivagina is preserved and provides for both hemivaginas. The vaginal septum is resected, and both hemivaginas are tubularized into a single vagina by taking advantage of the long lateral dimension of both hemivaginas. Then, what used to be the dome of the hemivagina where the hemiuterus was resected is turned down to the perineum (Figure 71.16). This is a useful maneuver that can be performed only when these specific anatomic characteristics are encountered.

Total or Partial Vaginal Replacement

In a patient with a small vagina or in the rare case of an absent vagina, a vaginal replacement is required. In such cases, the choices are rectum, colon, or small bowel. When the patient has internal genitalia or an upper blind vagina, the upper part of the bowel used for replacement should be sutured to the vaginal cuff. When the patient has no internal genitalia (no vagina and no uterus), a vagina is created and left with its upper portion blind and used only for sexual purposes.

Rectum

This form of vaginal replacement is feasible in patients who have a rectum that is large enough to be able to divide it longitudinally into a portion with its own blood supply that will form a new vagina and another portion with enough circumference to reconstruct an adequately sized rectum. The blood supply of the rectum will be provided transmurally from branches of the inferior mesenteric vessels. The distal rectum can also be used as a neovagina, with pull-through of the proximal colon as a neorectum, in patients that have poor prognosis for bowel

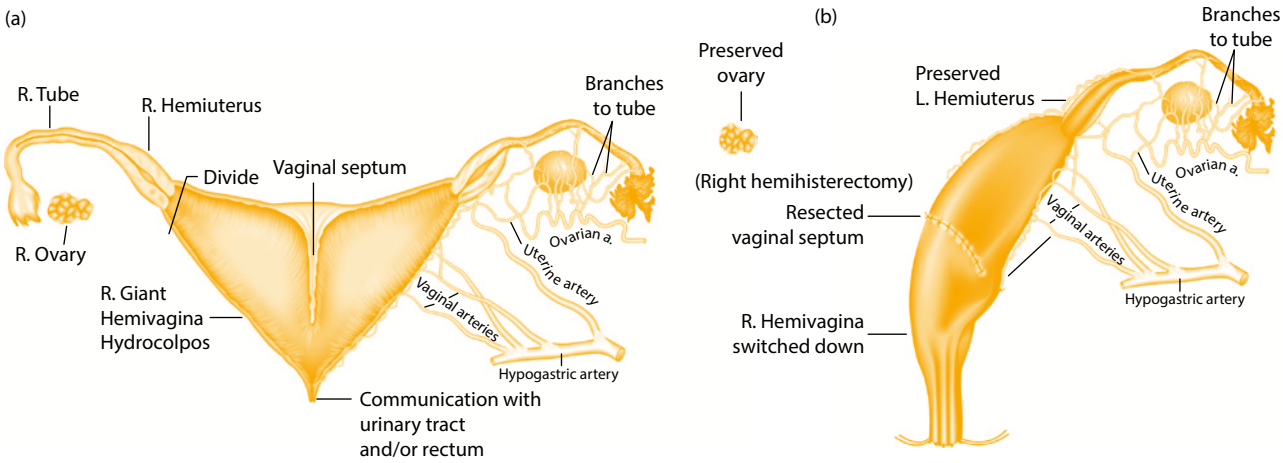

FIGURE 71.16 Vaginal switch procedure. (a) Anatomy required in order to use the vaginal switch maneuver. (b) Final anatomy after the vaginal switch maneuver.

control (sacral ratio <0.4). If the patient has good prognosis for bowel control, the rectum should be left as the rectum.

Colon

The colon is an ideal substitute to replace the vagina. However, sometimes the location of the colostomy interferes with this type of reconstruction. The left colon or sigmoid works well, as their arcades reach the perineum nicely. Sometimes taking the colostomy down and using the distal segment of it for the vaginal graft is a helpful maneuver.

Small Bowel

When the colon is not available, the most mobile portion of the small bowel is used for vaginal reconstruction. The mesentery of the small bowel is longer in an area located approximately 15 cm proximal to the ileocecal valve, which is the best portion of the small bowel for vaginal replacement. A portion of the ileum is isolated and pulled down while preserving its blood supply.

In the highest type of cloaca, one may find two little hemivaginas attached to the bladder neck or even to the trigone of the bladder. In these cases, the rectum also opens in the trigone (Figure 71.17). Separation of these structures is done abdominally. Unfortunately, when the separation is completed, the patient is frequently left with no bladder neck or a severely damaged one. At that point, the surgeon must have enough experience to make a decision of whether to reconstruct the bladder neck or close it permanently. In the first situation, most patients will require intermittent catheterization to empty the bladder. A vesicostomy is created in such cases, and the patient will require a continent diversion type of procedure and possibly a bladder neck procedure and/or bladder augmentation, done at the age of urinary continence (3–4 years old).

At the time of colostomy closure, endoscopy should be performed to be sure that the repair is intact and that there is no prolapse, stricture, or urethrovaginal fistula. If the cloaca repair did not require laparotomy, the time of colostomy closure is the opportunity to investigate the patency of the Mullerian structures when two hemivaginas and hemiuterii are present.

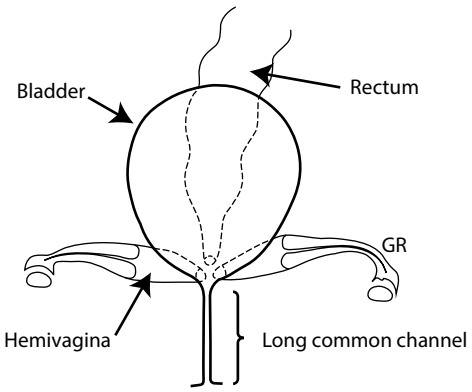

FIGURE 71.17 Highest type of cloaca showing the insertion of both hemivaginas and the rectum at the level of the trigone of the bladder.

NEUROPATHIC BLADDER

The mean incidence of neurovesical dysfunction in patients with ARMs is 35%. Table 71.1 demonstrates that the prevalence may vary quite widely among reported series.[12,15,61–64] As expected, high ARMs have the greatest incidence. However, neurovesical dysfunction can be present in children with low lesions. Therefore, we screen all patients with ARMs at birth with spinal sonography and a careful perineal exam. As previously noted, the recognition of the high incidence of occult spinal dysraphism has had a major impact on the management of these patients.[13–15,65] Such lesions may progress following surgical correction.[65–68] Although the timing of surgical intervention remains controversial, some authors suggest that early surgical intervention results in the best functional neurologic outcome.[69]

Screening ultrasonography has proven useful in the diagnosis of occult spinal dysraphism in infants.[70] Older children generally require MRI for diagnosis. The significance of these dysraphic states became apparent in the early 1990s. Early experience showed that dysfunctional voiding occurred in 31% and 5% of high and low ARMs, respectively. Structural spinal cord pathology was present in 12% and 4%, respectively.[15] One report from Appignani and colleagues suggested that screening by MRI for occult dysraphic myelodysplasia yields an even higher incidence of spinal cord pathology. They encountered dysraphic states in 17% of low ARMs, 34% of high ARMs, 46% of cloacal anomalies, and 100% of patients with cloacal exstrophy.[38] A study from Golonka in 2002 reported that 27% of those with high lesions and 50% with low lesions had a tethered cord by MRI.[71]

Some surgeons have wondered whether surgical correction of ARMs results in the development of the neuropathic bladder. Ralph, in 1992, evaluated 58 patients with imperforate anus who had reached an age of 18 years or greater. Of these, 43 patients had received rectal pull-through procedures, while the remainder received cutback procedures. They found evidence for a neuropathic bladder in 32 patients (55%). Ninety-one percent of these neuropathic bladders were hyperreflexic in nature.

TABLE 71.1 Incidence of neuropathic bladder in ARM

Series	No. patients	NVD (%)
Sheldon (1991)	90	24
Kakizaki (1994)	21	43
Boemers (1996)	90	57
Capitanucci (1996)	14	18
Emir (1998)	33	45
Borg et al (2009)	37	24
Total	285	35

Abbreviation: NVD, neurovesical dysfunction.

Thirty patients (52%) had spinal deformities, 21 (70%) of which had evidence for neurovesical dysfunction. Only three patients (5%) had hypotonic bladders, normal spinal anatomy, and high ARMs, and were felt likely to have iatrogenic neurovesical dysfunction.[72] Boemers et al., in 1995, evaluated 32 patients with ARMs who underwent PSARP employing urodynamic investigation. In 27 patients, urodynamic investigation was performed both before and after PSARP. No evidence of somatic nerve injury happened in this series. Detrusor failure suggestive of autonomic denervation occurred in three males, two of whom had combined PSARP with transabdominal dissection. The authors concluded that in the absence of transabdominal dissection and significant retrovesical dissection, PSARP did not affect lower urinary tract function.[73] De Filippo et al., in 1999, also reported that bladder dysfunction does not appear to follow a properly performed PSARP.[74]

Long-Term Urologic Follow-Up

The importance of long-term urologic follow-up to assess for neuropathic voiding dysfunction cannot be overemphasized, particularly in cases with risk factors that include hydronephrosis, VUR, tethered cord, abnormal sacrum, and urinary tract damage or denervation provoked during the repair of the ARM. In these types of cases, we consider that the follow-up must continue during the entire life.

Ideally, all patients, even those with normal kidneys, good sacrum, and normal spinal cord, should have a renal ultrasound at quarterly intervals in the first year postrepair and at yearly intervals after that. If the patient has UTIs and/or an abnormal kidney ultrasound, it will be necessary to do a full urologic evaluation, including a formal urodynamic study. Some investigators advocate a spinal MRI on all patients with ARMs given that spinal anomalies can occur even with low lesions.[75]

Depending on the results of such evaluations, patients may require a program of clean intermittent catheterization in order to protect the upper urinary tracts, as well as to be continent of urine. Patients with uninhibited detrusor contractions, poor compliance, and/or high bladder filling pressures may benefit from the addition of anticholinergic medication to their catheterization regimen. Ongoing collaboration with the colorectal team is important to adjust the bowel regimen if needed, as these medications are quite constipating.

Collaborative Approach to Surgical Reconstruction

A collaborative urologic and colorectal approach to reconstruction around the time of toilet training is in the best interest of the patient, as lower urinary tract reconstructive procedures can be combined with creation of a Malone appendicovesicostomy and sigmoid colon reduction, if indicated. Incidental appendectomy at the time of the initial surgical procedure must be avoided, because the appendix may be needed for either Malone antegrade continence enema (MACE) or Mitrofanoff neourethral bladder access.

Reconstructive Principles

1. Most neurovesical dysfunction and urethral strictures encountered in patients with ARMs are not iatrogenic but congenital in origin.
2. VUR is usually bilateral or, if unilateral, occurs in conjunction with a condition that threatens the contralateral kidney. In addition, neurovesical dysfunction often accompanies the VUR.
3. Initial management should be focused on identifying and correcting the bladder dysfunction rather than antireflux surgery. Ureteral reimplantation into a dysfunctional bladder usually fails unless the underlying bladder dysfunction is controlled.
4. Prompt and efficient decompression of obstructive hydronephrosis is essential in order to optimize long-term renal function.
5. Patients with ARM have a risk for latex allergy that is similar to that of the myelomeningocele population.
6. The combination of neurovesical dysfunction or urethral stricture with rectourinary fistulas predisposes the patient to critical neonatal illness, such as sepsis and hyperchloremic metabolic acidosis.
7. A low, fully diverting colostomy is most protective of the urinary tract.
8. Patients with a cloaca should never have their anorectal and urogenital sinus malformations corrected separately. The best results are attained by a single-stage PSARVUP. Those patients who present for correction of a urogenital sinus mesenchyme (UGSM) who have previously undergone an anorectal pull-through procedure are best corrected by reoperative PSARVUP complete with repeat mobilization of the rectum.

Renal Transplantation in Patients with Anorectal Malformations

Renal transplantation in the setting of ARMs and CM deserves additional comment. ESRD in this setting may dramatically complicate patient management.[16,76] Peritoneal dialysis is more difficult, or may be impossible, in the presence of multiple adhesions from prior transabdominal surgical procedures. Surgeons should make every effort to preserve the peritoneal cavity in the very young, because hemodialysis access is difficult and associated with long-term complications, such as superior vena cava thrombosis.

Renal transplantation in patients with ARMs and UGSMs is extremely challenging, as the majority of these patients with ESRD have major bladder pathology that must be controlled or corrected before transplantation, in order to optimize the allograft outcome. In addition, abdominal and pelvic vascular anomalies are relatively common in these children.[77] Successful renal transplantation, however, in the setting of imperforate anus and cloacal anomalies can be achieved, even after lower urinary tract continent reconstruction.[16,76,78]

LONG-TERM BOWEL FOLLOW-UP

Despite a successful initial surgical repair, approximately 25% of patients born with an ARM suffer from fecal incontinence. For those patients, we offer a bowel management program consisting of the administration of a specially designed enema that cleans the colon and allows the patient to remain clean of stool in the underwear for 24 hours.[79–81] The first step consists of ordering a contrast enema to evaluate and classify the colon in two groups:

1. Dilated colon with hypomotility (tendency to constipation)
2. Nondilated colon with hypermotility (tendency to diarrhea)

The first group will need a large and concentrated enema to clean the colon. The second group will need a small volume and nonconcentrated enema, but usually requires additional treatment, such as medication, to slow down their colon and a constipating diet. It generally takes 1 week, with trial and error, of modifying the enema recipe to find the specific enema that works for each child. During this 1-week bowel management program, abdominal x-ray films are taken on a daily basis in order to have an objective way to evaluate the effect of the enema.

Another important group of patients have bowel control but suffer from severe constipation. They should also be managed aggressively with oral laxatives. If the constipation is left untreated, the patients can have leakage from overflow fecal pseudoincontinence. The severe constipation can also have a negative impact in the urinary tract. After the bowel management has been successfully implemented, we discuss with the family the possibility of performing an operation to administer the enemas in an antegrade fashion. The continent appendicocecostomy was initially described by Malone and has revolutionized the care of patients with even the most debilitating malformations.[82,83] The procedure consists of connecting the cecal appendix, when available, or a cecal flap, known as neoappendicostomy, to the umbilicus and creating a one-way valve mechanism by placating the cecum around the appendix to allow the passing of a catheter and to prevent leakage of stool.[84–86] The technique can be modified to allow the appendix to be split and used for both an antegrade continence enema and a Mitrofanoff appendicovesicostomy.[87,88] A bowel anastomosis to harvest enteric tissue for a second catheterizable channel is thus avoided when enterocystoplasty is not indicated. We only offer this operation to patients in whom the bowel management has been successful. In a great deal of patients with nonneurogenic voiding dysfunction (urgency, frequency, and urge incontinence), we find that the urinary symptoms improve dramatically with better bowel management.[89]

CONCLUSION

Anorectal and CMs are highly complex diagnoses that can have lifelong implications to gastrointestinal, urinary, and reproductive health. A systematic and collaborative, multidisciplinary approach to management and treatment is highly recommended to achieve the best outcomes. Colorectal, urologic, and gynecologic surgeons should routinely meet and communicate to perform care coordination. The principles outlined in this chapter regarding the management of these conditions, along with the advancements in the science of perioperative surgical management and transplantation, have enabled even those children born with the most devastating congenital anomalies to be restored to health and a functional social status.

MULTIMEDIA FILES AVAILABLE ONLINE (www.crcpress.com/cw/Docimo)

VIDEO 71.1 Cine rotational fluoroscopic imaging of a cloaca patient with a 3 cm common channel.

VIDEO 71.2 Cine rotational fluoroscopic imaging of a cloaca patient with a 3.5 cm common channel.

VIDEO 71.3 Cine rotational fluoroscopic imaging of a cloaca patient with a 4 cm common channel.

VIDEO 71.4 Cine rotational fluoroscopic imaging of a cloaca patient with a 5 cm common channel.

VIDEO 71.5 Cine rotational fluoroscopic imaging of a cloaca patient with a less than 2 cm common channel.

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CHAPTER 72

Surgery for Intersex Disorders and Urogenital Sinus

Mark C. Adams, Romano T. DeMarco, and John C. Thomas

INTRODUCTION

Advances in surgical management have improved both the cosmetic and functional outcomes of patients with urogenital sinus abnormalities and those with varying degrees of intersexuality, at least when judged by treating surgeons. Early descriptions of methods such as clitoridectomy or convenient "forgetting" of the hypoplastic vagina are now considered archaic because of improved understanding of genital anatomy and function. Better exposure and innovative surgical techniques have produced surgical improvements, but while our understanding of these complex problems is indeed better, it is certainly not complete. Much remains to be learned about female genital function, the effects of surgery on genital innervation, and the significant psychological effects of these problems and their reconstruction on the patient.

GENITAL DEVELOPMENT AND IMPLICATIONS FOR SURGERY

Normal development in any organ system proceeds through a highly selective and complex cascade of interactions. Errors in development virtually always occur in a spectrum of severity and can lead to minor, inconsequential aberrancies or profound problems affecting patient survival. Embryologic errors in the urogenital tract similarly have a wide range of magnitude. Genitourinary embryology is discussed in detail in Chapter 14 of this text.

Under the influence of SRY (the sex-determining region of the Y chromosome), the bipotential gonad should differentiate into a testis near the seventh week of gestation. Normal phenotypic expression of male differentiation is then actively controlled by secretion of the Müllerian inhibiting substance (MIS) by Sertoli cells, and testosterone by Leydig cells. MIS causes rapid regression of the paramesonephric (Müllerian) ducts between the 8th and 10th weeks. In normal females, the absence of the Y chromosome and SRY protein secretion leads to the formation of ovaries without Sertoli or Leydig cells, and therefore the absence of MIS and androgens.

The paramesonephric ducts give rise to the fallopian tubes, uterus, and the upper two-thirds of the vagina. The distal third of the vagina is formed from endodermal tissue, the sinovaginal bulb. In these simple terms, the female phenotype was previously thought of as the passive or default sex, forming in the absence of the Y chromosome.[1] In fact, recent evidence suggests that specific genes, such as Wnt-4, are necessary for formation of the Müllerian duct, suppression of Leydig cell development during the indifferent stage, and maintenance of oocytes in the developing ovary.[2]

In a sense, normal males have a persistent urogenital sinus with ultimate entry of the Wolffian ducts, as well as a remnant of the Müllerian system at the veru montanum. It would therefore seem that the most proximal confluence of a persistent urogenital sinus in a female would be the area of the proximal urethra. While the vast majority of girls with a urogenital sinus anomaly have a confluence at that level or more distally, exceptions do rarely occur. The vagina may be found entering the bladder itself even cephalad to the level of the ureteral orifices. It is not known whether the Müllerian duct opening may migrate into the bladder in tandem with the ureteral bud or whether communication simply develops between the intimate structures.

Clearly, the normal vagina has two embryologic components. That complex development may contribute to the typical appearance of the vagina in the setting of a urogenital sinus. The distal portion of the vagina is virtually always narrow for a variable length (Figure 72.1). Recognition of that finding is critical in surgical reconstruction. Failure of flaps to reach all the way through the narrow segment and well into the more normal proximal portion may lead to stenosis. The paramesonephric ducts and entire Müllerian system are initially paired structures that should fuse distally in the midline. Errors in fusion do occur,[3] and patients with a persistent urogenital sinus or cloaca are at increased risk for such problems (Figure 72.2). In the setting of a urogenital sinus, the finding of a vagina to either side of the midline should arouse suspicion that a second vagina, even if obscure or obstructed, may well exist on the other side. Failure to recognize the second vagina at the time of reconstruction may eventually lead to hydrometrocolpos.

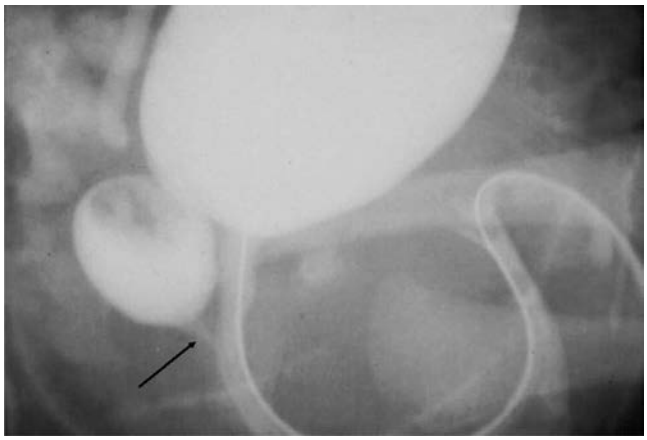

FIGURE 72.1 Genitogram on a female with a urogenital sinus. No matter the level of confluence, the distal vagina (arrow) is usually narrow.

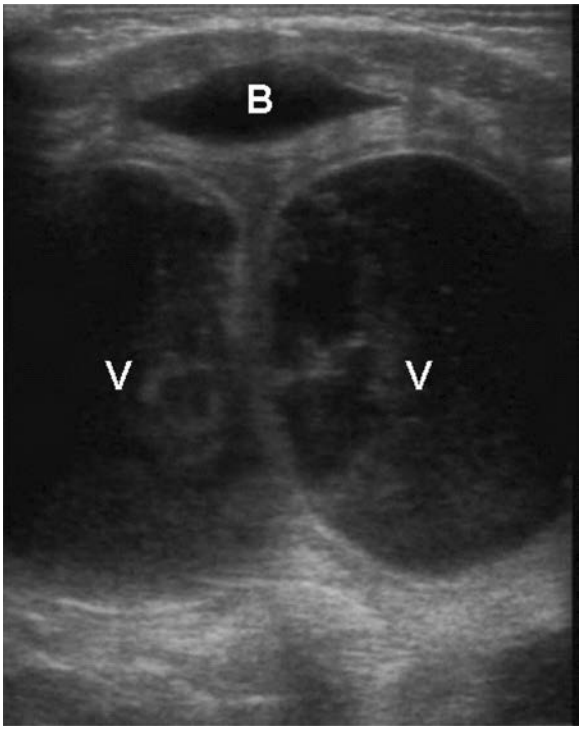

FIGURE 72.2 Postnatal ultrasound on newborn with urogenital sinus and duplicate vagina. Such vaginal distention with urine may be noted on antenatal studies. (B, bladder; V, vagina.)

CLASSIFICATION SCHEME

A urogenital sinus abnormality is present when a persistent communication occurs between the genital and urinary tract in the female. Typically, the urethra and vagina are joined and exit to the perineum as a common channel. If there is associated rectal involvement and imperforate anus, a persistent cloaca or cloacal anomaly exists with a single perineal opening for all three structures. A urogenital sinus with an anteriorly displaced rectum may represent the form früste of a persistent cloaca. Such a finding may have implications for rectal function and exposure during surgical reconstruction of the urogenital sinus. Patients with urogenital sinus anomalies commonly have associated abnormalities of the clitoris, labia, and external genitalia. In fact, the most common etiology of a persistent urogenital sinus is congenital adrenal hyperplasia (CAH).

The most useful classification schemes for urogenital sinus anomalies relate to the level of the confluence of the urethra and vagina. Hendren made a landmark contribution to genital reconstructive surgery when he divided urogenital anomalies into those with a confluence above or below the female external sphincter and suggested that a different surgical approach was indicated for the two types.[4] In females with extreme virilization related to CAH, the external sphincter may be well developed and quite obvious. In most females, the sphincter mechanism may be indistinct and the level of the pelvic floor a more reliable landmark. The absence of a well-defined external sphincter in such patients has led to subjective classification based on the level of confluence as low, moderate, or high. It is important to recognize that the level of confluence should be considered relative to the bladder neck and not the external meatus. Virilization of the distal urethra or urogenital sinus may create a confluence that is distant from the meatus yet still relatively low. The critical determinant is therefore the distance from the bladder neck to the confluence as it affects reconstructive surgery (Figure 72.3). Rink et al.[5] have proposed a more rigid classification scheme based on careful measurements from both directions.

The nature of the urogenital sinus distal to the confluence should also be considered. Hendren described the urogenital sinus distal to the confluence as urethra-like or vagina-like based on circumference.[6] This difference has typically been applied in descriptions of a persistent cloaca but may be useful for isolated urogenital sinus anomalies as well. The difference between the two has

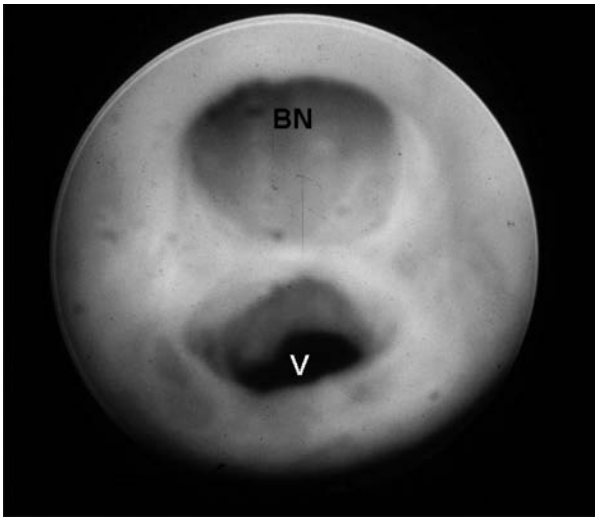

FIGURE 72.3 Endoscopy. A vaginal (V) opening this close to the bladder neck (BN) represents a high confluence no matter the distance from the external meatus.

potential influence on surgical reconstruction in terms of the amount of local tissue available for reconstruction of the urethra or vagina.

EVALUATION

A thorough evaluation of the newborn with a urogenital sinus should be completed expeditiously. Immediate attention to and stabilization of any fluid or electrolyte imbalance is paramount. Delays in appropriate medical evaluation of those patients with CAH and unrecognized salt wasting carry significant risks. Initial screening studies in such patients include assessment of serum electrolytes, biochemical assay screening for CAH, and evaluation of karyotype using cultured peripheral leukocytes. A multidisciplined assessment is initiated, including medical professionals from neonatology, endocrinology, child psychiatry, medical genetics, urology, gynecology, and at times, medical ethics. Gender assignment based on karyotype and potential for genitourinary function should be made after discussion within the entire treatment team and the parents. A child should not be named until the appropriate gender assignment is made.

History and Physical Examination

A careful maternal and family history is mandatory. Maternal use of alcohol or drugs and exposure to androgenic substances, as well as a family history of previous neonatal death, infertility, genital ambiguity, abnormal pubertal development, or inguinal hernias associated with retained Müllerian structures, may contribute to proper diagnosis.

Physical examination of the child is important and may provide further clues. The general well-being of the child should be assessed. Signs of dehydration and lethargy suggest a diagnosis of CAH. Blood pressure should be evaluated since hypertension can be found in patients with 11-β-hydroxylase deficiency. The abdominal exam should note any lower, midline abdominal masses, which might represent a distended bladder or vagina. The back should be assessed for any findings associated with an underlying neurologic anomaly. Gonads are palpated to determine their location, number, and size and associated structures, such as an epididymis and vas deferens. Rectal examination should carefully evaluate the location of the anus, and palpation with the little finger may identify the midline cervical cap or uterine tissue. Careful inspection of the female introitus is required to identify an isolated urogenital sinus if no clitoral or labial abnormalities are present.

Radiographic Evaluation

Ultrasound is a valuable adjunct to physical examination in these patients. The newborn period is the optimal time for evaluation because maternal hormones make the ovaries and uterus more prominent.[7] The spinal cord may also be evaluated to rule out cord tethering. While sometimes helpful, the sensitivity for locating a nonpalpable or intra-abdominal gonad with sonography is at best 60%.[8] Hydrocolpos, in this setting usually related to retained urine, and bladder distension are easily seen with sonography. Likewise, the kidneys should be evaluated for hydronephrosis, dysplasia, and agenesis. Additionally, patients with CAH usually have a cerebriform appearance of their adrenal glands, which may be helpful in diagnosis.[9]

All patients with a urogenital sinus anomaly should undergo contrast genitography. These studies require interest, skill, and determination on the part of the radiologist. The study may be performed by insertion of the tip of a Foley catheter into the opening of the urogenital sinus. The balloon may then be inflated outside the meatus to prevent spillage of contrast, and retrograde instillation of radiopaque dye used to define the anatomy. In many cases, it is then possible to advance a feeding tube into the bladder for formal voiding cystourethrography. Proper studies can define the length of the common sinus and the level of confluence.

Magnetic Resonance Imaging

Although the above-mentioned studies are used to evaluate urogenital sinus abnormalities after the child is born, fetal MRI can give distinct anatomic details that may allow for more accurate postnatal counseling when a cloacal anomaly is suspected on ultrasound. Cloacal malformations can be suspected on MRI with a high degree of certainty in the presence of a multicystic pelvic mass, abdominal ascites from retrograde flow of urine via the fallopian tubes, a dilated bladder, hydrocolpos, or hydrometrocolpos. Small rectovesical fistulas can be difficult to see on fetal MRI; however, meconium extending below the level of a pelvic cystic mass supports the diagnosis of a urogenital sinus. In addition, associated renal and limb anomalies can also be identified.[10]

MRI is especially helpful in the evaluation of Müllerian anomalies, which are common with urologic anomalies and disorders of sex differentiation. The sensitivity of pelvic MRI for detection of a Müllerian duct abnormality ranges from 77% to 100%.[11] For patients with Mayer–Rokitansky–Kuster–Hauser, pelvic MRI can confirm the absence of the midline uterus and assess the presence of uterine remnants, which may be obstructed. The most sensitive time for detection of Müllerian duct remnants is during puberty, as the uterine structures grow with estrogenization. Attempt to delineate uterine structures prior to puberty by MRI has been associated with misleading diagnoses, as the uterus is small and may be difficult to visualize.[12] In any patient with a cloaca, dysmenorrhea is an indication for evaluation of an obstructed uterine horn, which may not have been identified during prior prepubertal operations.

Endoscopic Evaluation

Endoscopic evaluation of the anatomy is critical and should be performed on all children with a urogenital sinus. Generally, this is done under the same anesthetic as open reconstruction, particularly for lower or intermediate lesions. If the anatomy is not well understood after

radiographic evaluation, particularly in the presence of a high confluence or after failure to identify any vaginal structure on genitography, cystoscopy may be performed alone in order to better understand or delineate the anatomy and better prepare the patient and family for reconstructive surgery. Careful endoscopy is generally more accurate than genitography in defining the true level of confluence.[13]

Further Studies

In rare circumstances, usually related to the diagnosis of intersex, the definite diagnosis may remain elusive after conventional studies. At times, hormonal stimulation to evaluate the presence and function of testicular tissue may be indicated. Gonadal biopsy may be necessary for diagnosis. An adequate biopsy requires a full-length, deep longitudinal incision into the gonad to ensure adequate tissue sampling. This may be done in an open fashion or laparoscopically. Such a procedure allows for thorough examination of the pelvis and abdomen for Müllerian and Wolffian structures.

Timing

Significant improvements in surgical techniques and outcomes have occurred over the past several decades. Despite these apparent improvements, controversies remain. Intersex advocacy groups, patients, and some medical professionals still question the timing of surgery and whether reconstruction should be performed at all until the patient can contribute to informed consent. Discussions with a multidisciplinary team and parents must address these controversies prior to female genital surgery. Today, most genital reconstructive surgery is performed in congruence with genetic sex. Only in very rare situations is gender conversion considered.

Most girls with a urogenital sinus diagnosed as infants have CAH. Waiting several months allows good stabilization of the patient from an endocrine and metabolic standpoint. Appropriate medical treatment will, at times, produce improvement in the external virilization but seldom result in complete normalization. Relatively early intervention may carry the benefit of thicker, more vascular skin and easier dissection or manipulation of the clitoris and paravaginal tissue related to maternal estrogen stimulation. There may also be some psychological benefit for the parents from early correction of the virilized external genitalia.

The optimal age for vaginal reconstruction is also controversial. Total genital reconstruction with vaginoplasty has most often been performed as a single stage with clitoroplasty within the first several months to first year of life. This has been particularly true for patients with CAH, most of whom have clitoromegaly and a low to moderate confluence of the urogenital sinus. Potential benefits include improved tissue transfer and reduced scarring secondary to estrogen stimulation, minimization of parental anxiety over the child's condition, and earlier self-acceptance of the child's gender identity and genital anatomy. It must be noted that delayed vaginal construction has been recommended by some surgeons.[14] Early vaginal reconstruction may carry some increased risk of vaginal stenosis when evaluated in the adolescent or young adult.[15] Advocates for delayed reconstruction note the psychological concerns in older patients with subsequent vaginal stenosis, particularly when vaginal dilation is required. It is not clear that later, major reconstruction for vaginoplasty will carry a lesser psychological impact on the patient. We strongly favor complete, early repair, as we have found the exposure and surgical reconstruction then to be considerably easier than in an older patient, and value the availability of genital skin from the clitoris for vaginal reconstruction.

Patient Preparation

Most children undergoing vaginoplasty for a urogenital sinus anomaly, unless the confluence is extremely low, undergo a full bowel preparation using polyethylene glycol-electrolyte solution (Go-LYTELY, etc.). For young children, this preparation is done as an inpatient, with bowel catharsis administered by a nasogastric tube. Adolescent patients may self-administer the bowel preparation orally at home with parental guidance. A series of oral antibiotic doses are often administered, as well as perioperative broad-spectrum intravenous antibiotics.

After general anesthesia is administered, the child is usually placed first in the dorsal lithotomy position for endoscopy. Even if endoscopy has previously been performed in the newborn period, we generally repeat endoscopy at the time of surgical reconstruction, as the internal genital findings may be much more obvious in an older patient. The rectum and distal colon may also be irrigated clear of any residual fecal matter at this time. For higher lesions, a Foley catheter is placed into the bladder, and a second catheter, either a Fogarty or Foley, is placed into the vagina. Cystoscopy aids in confirmation of catheter placement in the appropriate position.

Surgical preparation is dependent on the extent of the planned reconstruction and surgical preference, as well as the age of the patient. In all but the lowest of urogenital lesions, we perform a full, lower body prep from the nipple to toes, front and back (Figure 72.4). The catheters are kept sterile and prepped into the surgical field. The feet and lower legs are wrapped, and the patient passed through an aperture in the surgical drape. This preparation allows exposure to the entire lower body in both the prone and supine positions. It is simple and safe to move smaller patients between the two positions. It is often helpful to perform the external feminizing genitoplasty with the patient supine while exposing and repairing the proximal sinus in the prone position. Trying to prep and move a larger teenage patient in a similar fashion may be cumbersome and impractical. If prone positioning is desired for exposure and vaginoplasty in such patients, a modified skydiver position may be used. Positioning and padding must be utilized carefully to avoid injury.

Feminizing Genitoplasty

The surgical management of the child with clitoromegaly has undergone marked evolution from early methods

FIGURE 72.4 Lower body preparation. The preparation allows a supine and prone approach. Smaller patients may be easily turned between the two positions.

advocating clitoral amputation.[16,17] While satisfactory cosmetic results were reported after such procedures,[18] impairment in orgasm and psychosexual development were later noted.[19] The first attempts at sparing the clitoris with modification of the appearance involved clitoral recession or concealment.[20–22] All current techniques have as their cornerstone preservation of clitoral sensation and function and are influenced by Schmid's landmark description of corporal body excision and neurovascular bundle conservation.[23] Early reports described complete excision of the corpora cavernosa of the phallus, including the tunica, while the neurovascular bundle was preserved only with Buck's fascia.[24] It then became clear that subtunical resection of the corporal erectile tissue with preservation of the dorsal tunica might protect the glanular nerve and blood supply.[25] Recently, Baskin and colleagues have suggested that a more ventral tunical incision may be prudent after carefully demonstrating lateral fanning of the clitoral nerve supply.[26] Other interesting work has helped define the spatial relationship of the normal clitoris, urethral meatus, vaginal introitus, and other anatomic landmarks,[27] as well as begun to examine which areas of external genital skin may be most involved in genital sensation and orgasm.[28]

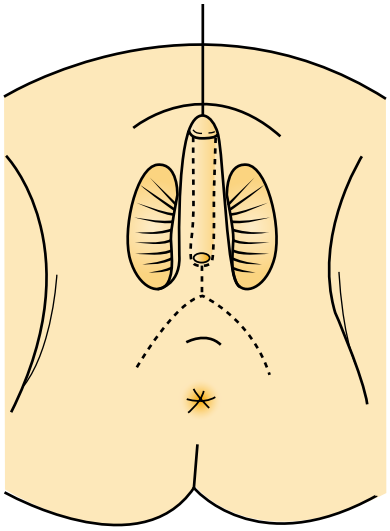

FIGURE 72.5 Feminizing genitoplasty. (a) The dashed lines mark the initial incisions. (b) After mobilization of the skin and posteriorly based flap, the clitoris and sinus are exposed.

Clitoral resection is performed with the child supine with legs spread or in a low lithotomy position. A traction suture is placed in the glans clitoris, and the initial incision is marked and made in a circumcising fashion just off the glans over the dorsum and lateral aspect of the clitoris. Ventrally, the incisions are carried in a parallel fashion from distal to proximal on either side of what would be the urethral plate (Figure 72.5). These incisions are carried proximally to and around the meatus of the sinus. The lines of incision and base of the clitoris may be infiltrated with 1:200,000 epinephrine with or without lidocaine for aid in hemostasis. Incisions are carried down to Buck's fascia and the clitoris degloved of phallic skin. The urethra is generally left attached to the glans with consideration of glanular blood supply, while the urethral plate with spongiosum is dissected off of the corpora cavernosa to expose the ventral tunica of the cavernosa.

The tunica of the corpora are incised proximally at their bifurcation on the ventromedial side (Figure 72.6). Longitudinal incisions are carried out toward the glans all the way through the tunica to exposure of the erectile tissue. Erectile tissue is then sharply excised from the proximal bifurcation out to the level of the corona, along with the ventral tunics. The proximal ends of erectile tissue may be oversewn or suture ligated for hemostasis. Even after treatment with steroids, the glans clitoris may be remarkably enlarged. If so, the glans may be reduced by excising a wedge of glanular tissue on the ventral surface. Baskin et al. have shown that ventral excision of the glans is the most appropriate when considering the nerve supply.[26] The reduced glans should be approximated to the base of the corporal bodies by anchoring sutures. The location of the glans should give consideration to the position of the clitoral hood and symphysis pubis.

Feminizing genitoplasty also involves construction of labia minora from clitoral skin, as well as modification of the labia majora (Figure 72.7). The phallic skin

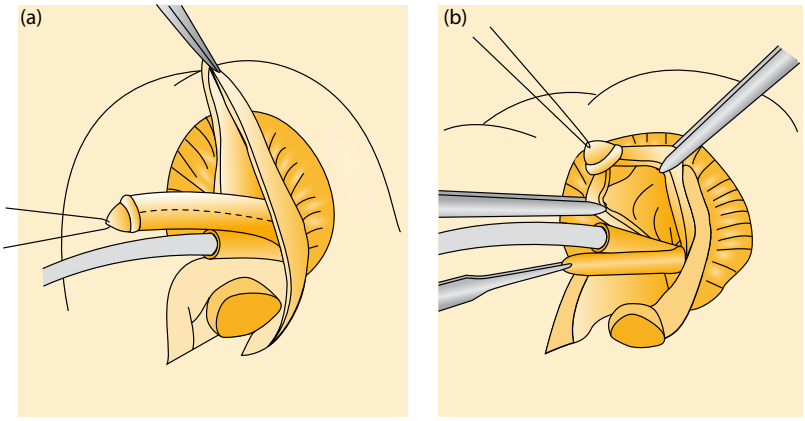

FIGURE 72.6 Corporal reduction. (a) The urethral plate and spongiosum are mobilized off the ventral corpora. The dashed line shows the ventromedial incision into the tunica on either side. (b) The erectile tissue is excised with ventral tunica.

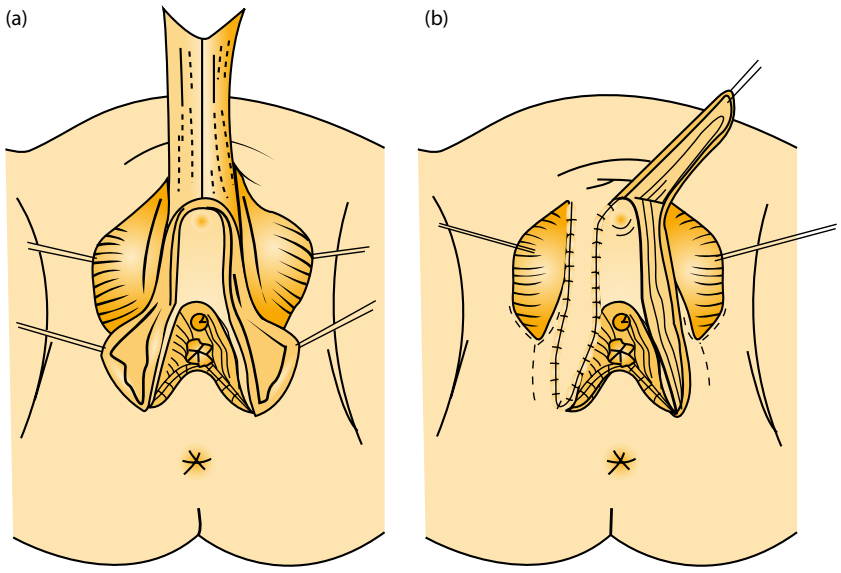

FIGURE 72.7 Labioplasty. (a) Redundant dorsal phallic skin is mobilized and incised in midline. (b) The phallic skin is used as labia minora on either side. Y-V plasty is performed on the labia majora. The posterior flap is advanced into the vagina.

is released dorsally and unfurled by mobilizing the inner from the outer prepuce. The skin is then usually incised in the dorsal midline. The midline incision is stopped short of the base of the phallus in order to preserve an appropriate hood over the dorsal clitoris. The excess skin is rotated ventrally, trimmed, and approximated to either side of the urethral plate medially, as well as the modified labia majora laterally. The flaps, as such, can serve as labia minora. Alternatively, the phallic skin may be used for an anterior vaginal flap in more proximal repairs. The labia majora, as the result of virilization, are often initially short and rounded. An aggressive incision around the medial, posterior, and lateral aspects of the labia majora on either side allows the labia to be lengthened and narrowed using a Y-V plasty. This plastic reconstruction of the labia is often performed in conjunction with flap vaginoplasty, and modifications in the posteriorly based vaginal flap may allow the labia from either side to swing inward posteriorly and avoid an overly wide posterior introitus.[29]

Surgical Correction of the Low Confluence

Cutback Vaginoplasty

A cutback vaginoplasty is a simple procedure performed in the patient with labial fusion. This technique involves incision of the fused skin posteriorly to the perineum to expose the vaginal orifice. The incised lateral edges are oversewn. While such a procedure is simple and may produce a good result in the appropriate patient, it is only a consideration in patients with a common urogenital sinus on the phallus with confluence of a normal vaginal opening at the level of the perineum. That combination is extraordinarily rare; thus, the procedure is very rarely, if ever, indicated.

Flap Vaginoplasty

Flap vaginoplasty is best suited for those patients with a low confluence of the urogenital sinus. The perineal skin incision is marked and made as a broad-based, inverted

U flap.[30] The closed end of the flap is created at the posterior lip of the meatus of the urogenital sinus, and the lateral margins should be well inside the ischial rami. The flap may be variable in length, depending on the length of the urogenital sinus; however, the posterior extent should leave a normal-sized perineal body. Design of the flap should respect considerations of length versus width so as to ensure a good blood supply. Maintaining a U rather than narrow V shape at the tip anteriorly helps to make sure that the end of the flap is not ischemic. The skin flap should be mobilized away from the posterior aspect of the urogenital sinus while maintaining a thick layer of subcutaneous tissue and fat with the flap. This mobilization exposes the urogenital sinus, which is eventually incised in the midline posteriorly. The incision is carried into the vagina and must extend through the distal vagina, which is typically narrow. Failure to place the flap well into the proximal vagina, which is normal in circumference, may result in stenosis, as can ischemia at the distal end of the flap. The flap of perineal skin is advanced into the vagina and secured with interrupted absorbable suture and should reach without tension (Figure 72.7).

The broad-based flap may create an abnormal appearance to the introitus posteriorly when the labia are spread. Careful trimming of the dermis and epidermis at the base of the flap may allow creation of a rhomboid or omega shape without sacrificing viability of the flap (Figure 72.8).[29] Such excision at the base should only remove skin elements but not the underlying subcutaneous tissue. Modification of the flap allows subsequent use of the labia to provide some posterior closure of the introitus and a more normal appearance. Posterior excision of the skin should not be so extreme as to compromise the vascularity of the flap, and the subcutaneous tissue must be carefully preserved at that level.

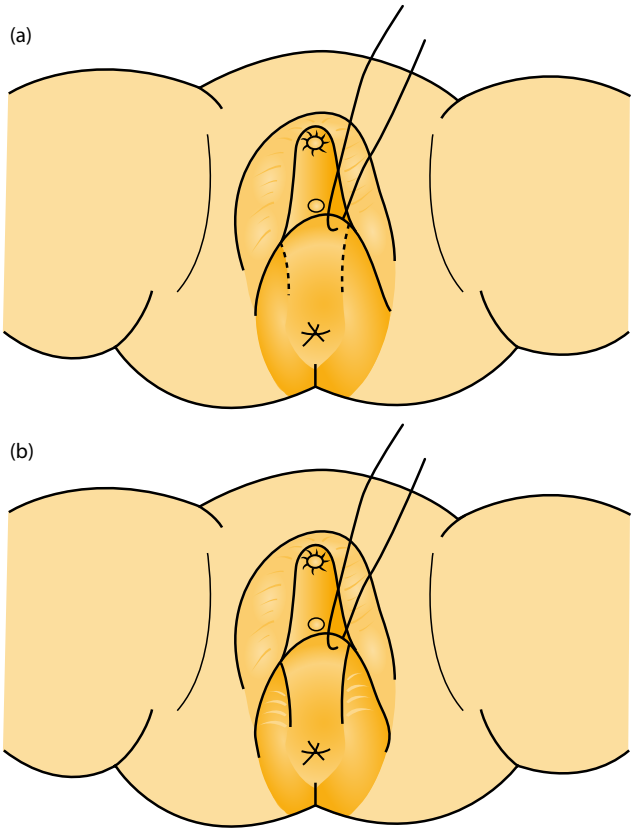

FIGURE 72.8 Omega flap. Skin elements may be excised carefully at the base of the flap to create a more normal-appearing posterior introitus. Subcutaneous tissue and blood supply should be preserved at the base.

It should be noted that flap vaginoplasty does not totally correct the urogenital sinus. Without any separation of the vagina from the urethra and lengthening or advancement of the urethra itself, the patient is still left with a urogenital sinus. The sinus, however, is much broader distally, and may therefore not be of any functional or cosmetic significance. Consequently, flap vaginoplasty should not be a viable surgical option for correction of a high-confluence urogenital sinus. One appropriate role for total urogenital mobilization may be to advance the level of confluence toward the perineum in a patient with a moderate-level lesion in order to make conventional flap vaginoplasty an appropriate technique for repair.

Surgical Correction of the Higher Confluence

Pull-Through Vaginoplasty

This repair, as described by Hendren and Crawford,[4] was a landmark advance in female genital reconstructive surgery; its basic principles still apply for children with higher lesions. Hendren's initial description includes the use of shallow, opposing U-shaped incisions on the perineum at the spot for placement of the eventual vaginal introitus (Figure 72.9).[4,30] Dissection is then made parallel and slightly posterior to the distal urogenital sinus until the vaginal catheter is encountered. A finger placed in the rectum may help maintain the proper plane of dissection posteriorly. The vagina is divided at its entrance to the sinus and then mobilized extensively. The proximal urogenital sinus at the site of prior confluence is closed, and the urogenital sinus used as a functional urethra. As originally described, the vagina is mobilized extensively in a circumferential fashion. The proper plane of dissection between the proximal urethra and anterior vagina is always quite difficult. For the first several millimeters, there is often virtually no connective tissue between the mucosa of the two structures. Dissection must continue through this difficult area in order to achieve adequate mobilization, and Hendren[4] and others[31] initially promoted mobilization of the vagina to the extent that it could be advanced as is to the perineum. Avoidance of the bladder and urethral sphincter mechanisms is mandatary as one proceeds proximally. In general, it is better to err by dissecting too close to the vagina than on the side of the bladder or urethra. This method is technically challenging, largely due to limited exposure to the critical area of the confluence. Early results produced an isolated and separate vaginal opening that is cosmetically unappealing. Additional problems related to vaginal stenosis have been reported and may be due to tension created by attempts to mobilize relatively thin vagina all the way to the perineum.[32]

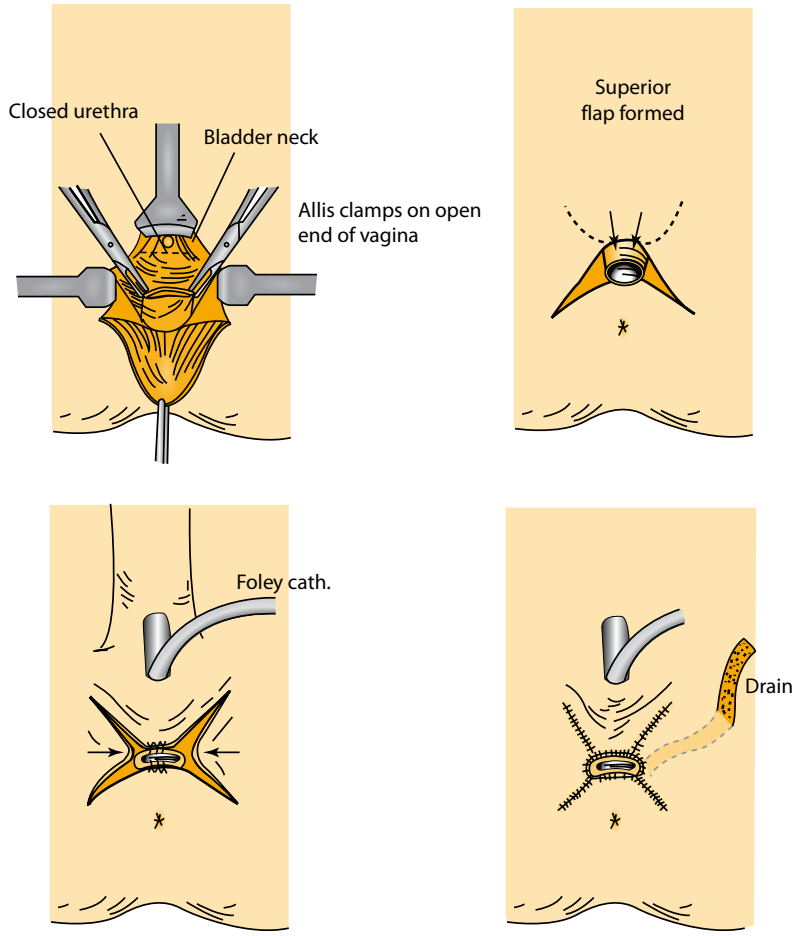

FIGURE 72.9 Pull-through vaginoplasty. The vagina is mobilized off of the urogenital sinus and advanced to the perineum. The sinus is closed as urethra.

Exposure

Much of the difficulty with pull-through vaginoplasties was related to exposure of the high confluence, and modifications have been described to improve the approach to the critical proximal area. Passerini–Glazel, in 1989,[32] popularized Monfort's transtrigonal approach in which the vagina is approached from a midline incision in the posterior wall of the bladder. It does provide superb exposure to a very high lesion but is usually not necessary. During dissection from below, simple incision of the posterior wall of the entire urogenital sinus from the meatus to the level of the confluence may improve exposure over that achieved when leaving the distal portion intact. Opening of the entire sinus then necessitates subsequent tubularization of the same structure for use as a urethra and theoretically increases the length over which a urethrovaginal fistula may occur. Most such fistulas, however, when they occur, do so at the level of the initial confluence where the exposure and repair are most tenuous. Anything done to improve exposure and the quality of the repair at that level may ultimately be advantageous. This extended incision into the sinus is particularly beneficial when the distal anomaly is vagina-like. Such a lesion requires tapering distally to achieve a more normal urethra.

The persistent cloaca is a more complex lesion than a urogenital sinus because the rectum is also involved. Cloacal anomalies are generally approached and repaired through a posterior sagittal incision extending from the coccyx. Once the rectal fistula has been removed and the more proximal rectum mobilized, the patient is left with a urogenital sinus that is nicely exposed through an incision that is much longer in the sagittal axis. Reports do exist of a posterior sagittal approach to a high urogenital sinus with splitting of the rectum either completely or anteriorly.[33] Such exposure is superb but potentially adds morbidity and is generally not necessary. Rink et al.[34] encouraged use of an anterior sagittal prone approach without division of the rectum. This approach provides excellent exposure during the difficult mobilization of the vagina off of the posterior urethra and bladder neck and does not preclude use of an inverted U-shaped incision as described for flap vaginoplasty. The procedure begins with the child supine, and the initial steps of clitoroplasty, if necessary, are performed. Initial dissection onto the posterior aspect of the more distal sinus is begun in the supine position. The patient, prepped from nipple to toes, front and back, is then turned prone. The dissection, with remarkably better visualization after the change in position alone, is continued between the posterior wall of the urogenital sinus and the rectum in the midline. The intact rectum is displaced superiorly with a malleable retractor, and the urogenital sinus is opened well into the vagina

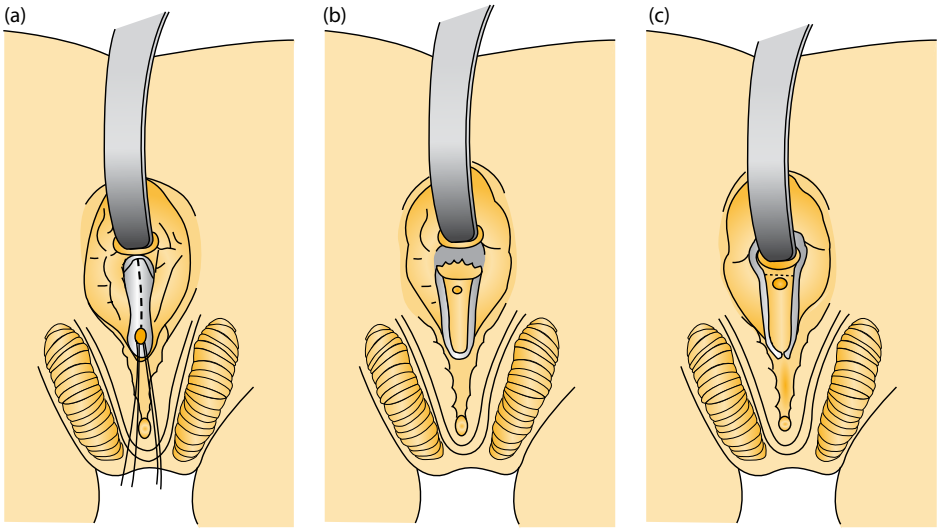

FIGURE 72.10 Prone exposure to high confluence. (a) After creation of a posteriorly based flap, the rectum is retracted to expose the sinus. (b) The sinus is opened into the vagina. (c) The malleable retractor is placed into the vagina to expose the critical area of dissection (dashed line).

(Figure 72.10). The same malleable retractor can then be placed into the vagina to provide excellent visualization anteriorly. Following aggressive anterior vaginal mobilization, the urogenital sinus is closed in several layers over a urethral catheter, creating a neourethra. Generally, several layers of tissue can then be approximated in the midline to separate the vagina and urethra.

Complex Flaps

It is often clear that the short vagina mobilized off of the urethra in a patient with a high-level urogenital sinus may not reach the perineum without tension. The use of flaps to reach the proximal vagina may provide the potential to improve the functional and cosmetic result of pull-through vaginoplasty. Complex flaps of labia majora or buttocks skin from either side may be used to reach the proximal vagina without tension.[35] Such flaps may provide a good result from the standpoint of a functional vagina but can distort the appearance of the introitus. Secondary perineal surgery 6–12 months after initial creation of the flaps may be appropriate to divide the base of such flaps and re-create a more normal appearance of the labia and perineum. Gonzalez and Fernandes[36] used flaps of phallic skin to construct the distal vagina. Passerini–Glazel[32] used the distal urogenital sinus opened anteriorly rather than posteriorly in a similar fashion. The sinus was folded back at the proximal end of the anterior incision and combined with phallic skin to tubularize as a distal vagina. Such flaps of clitoral skin or distal urogenital sinus may be useful in constructing the anterior vagina in combination with a posteriorly based, U-shaped flap. Rink and Cain[37] have recently described lateral incision into the distal urogenital sinus with spiral construction of a distal vagina that is mucosally lined at the level of the introitus (Figure 72.11).

Total Urogenital Mobilization

In 1997, Pena described the technique of total urogenital mobilization for repair of urogenital sinus in patients with a cloacal anomaly.[38] Applications for this repair were soon expanded to include patients with urogenital sinus abnormalities alone. Such mobilization is generally not necessary for patients with a low confluence, and the best indication for its use may be patients with a midlevel lesion in whom the level of confluence may be converted to a low one suitable for flap vaginoplasty. The role of total urogenital mobilization for patients with a very high lesion remains to be determined. Total urogenital mobilization may just be used in such patients to improve exposure at the critical level of confluence. The urethra and vagina can be mobilized toward the perineum and separated, and the structures released back to a proximal position for reconstruction. Total urogenital mobilization for high lesions with advancement of the confluence to the perineum has also been described; however, long-term validation of the results in such patients needs to be determined. Potential advantages of this technique include improved cosmesis, easier dissection leading to decreased operative time, and less risk of vaginal stenosis or urethrovaginal fistula.[38] There is no question that this operative technique with advancement is potentially easier, as it avoids the difficult dissection between the anterior vagina and proximal urethra or bladder neck; an easier operative approach, however, does not necessarily mean a better long-term result for the patient. Rare patients with a urogenital sinus, particularly those related to the persistent cloaca, may suffer from urinary incontinence or poor voiding. Such dysfunction may be related to the anatomic problem, abnormal innervation, or a combination of the two issues. Circumferential dissection of the urogenital sinus to the bladder neck potentially could exacerbate neurologic problems. Even if it does not do so in the short term, long-term follow-up of girls with high lesions undergoing total urogenital mobilization with advancement distally will be required to examine the risk of stress urinary incontinence.[39,40] Stress incontinence in patients after such a procedure would likely be very difficult to treat.

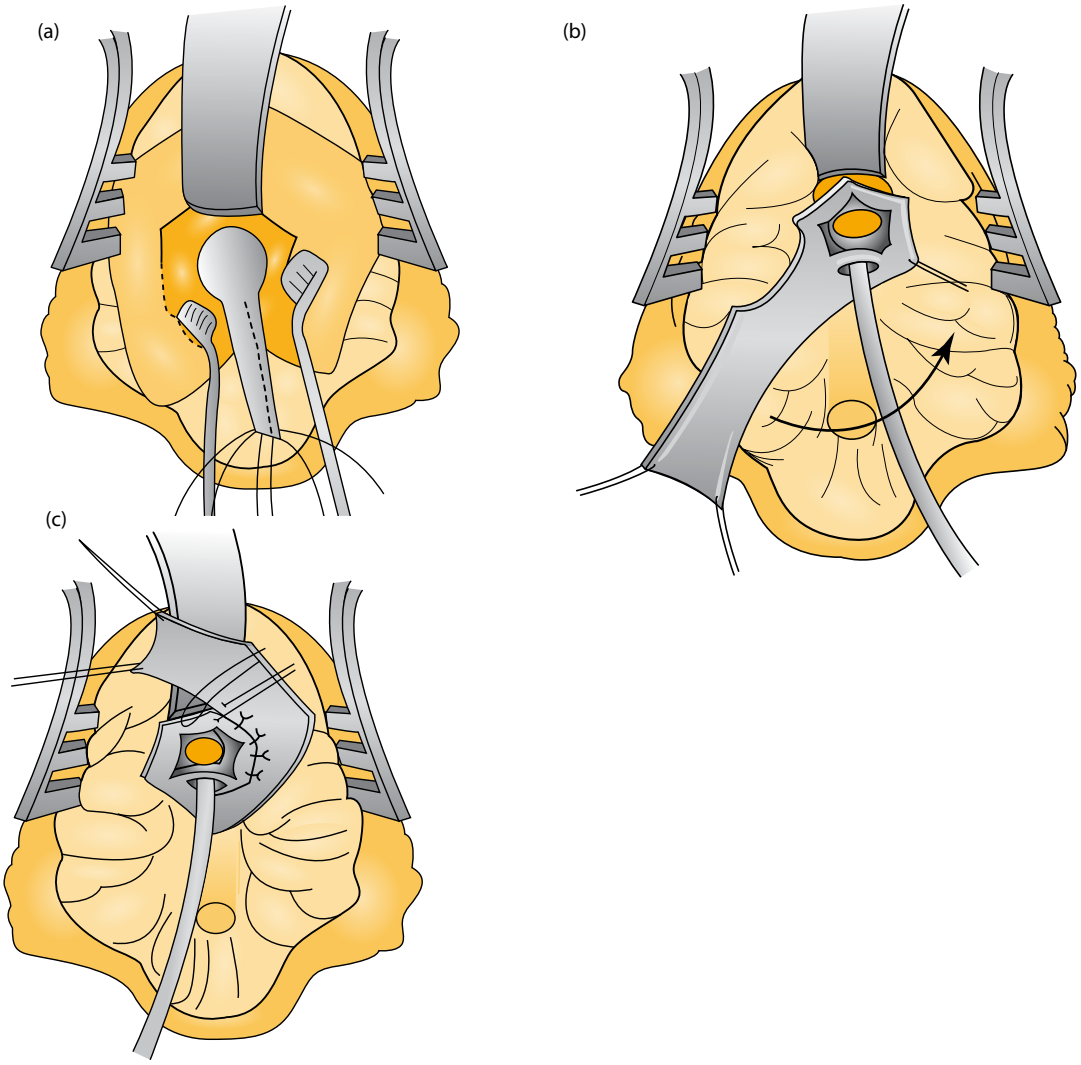

FIGURE 72.11 Use of distal sinus for vaginoplasty. (a) After total urogenital mobilization and exposure of the confluence, a lateral incision in the sinus (dashed line) is planned. (b) A healthy flap is created opposite the side of the incision. (c) The flap can be utilized in a spiral fashion to create a distal vagina.

In total urogenital mobilization, the sinus is initially approached from the midline posteriorly, and attachments between the rectum and sinus divided. This exposure may be done from a midline incision or after creation of a posteriorly based flap. The sinus is then circumscribed at the meatus on the clitoris and dissection carried circumferentially from distal to proximal. The distal sinus is carefully mobilized with all spongiosum off of the corpora cavernosa (Figure 72.12). Anteriorly, the ligamentous attachments of the sinus to the pubis are incised, allowing for adequate mobilization to the perineum. It is possible in some cases that anterior dissection may be stopped just short of these attachments.[41] The catheter in the vagina is palpated, identifying the posterior vaginal wall. The vagina is opened posteriorly between stay sutures well through the distal narrow segment. If the vagina reaches the perineum without tension, the sinus can be opened ventrally to create the vestibule. A posteriorly based flap may be useful in some such cases. If the vagina is very high and the urethra very short above the confluence, a decision must be made on whether advancement of the intact sinus toward the perineum is appropriate (Figure 72.13). If not, the patient may be turned to the prone position and the vagina separated from the sinus. The distal mobilized sinus may then be incised dorsally or laterally, as previously described,[32,37] and used for vaginoplasty after the more proximal sinus is tubularized as the urethra. The child is usually turned back to the supine position to complete the plastic repair of the labia and perineum. Bladder catheter drainage and vaginal packing are usually employed after such complex repairs.

Partial Urogenital Mobilization

Proximal circumferential dissection of the urogenital sinus can increase the risk of sphincteric musculature or nerve injury. Partial urogenital mobilization (PUM) was introduced by Rink and Kaefer as an alternative to manage most confluences, with the exception of the very high anomalies. The circumferential dissection may be stopped anterolaterally at the level of the pubourethral ligament and potentially avoid injury to the sphincteric complex or its nerve supply.[42]

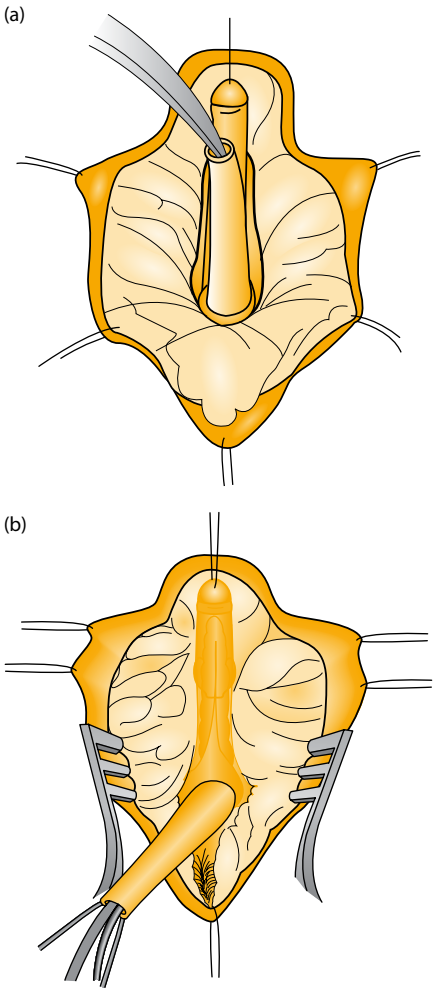

FIGURE 72.12 Total urogenital mobilization. (a) The skin is mobilized and the sinus exposed with a circumferential incision at the meatus. (b) The sinus is mobilized from the rectum posteriorly and the corpora anteriorly up to the pubis.

Vaginal Replacement

Dilation and Traction

In 1938, Frank described progressive dilation of the vaginal dimple with a dilator and manual pressure.[43] Ingram modified this technique in an attempt to minimize patient fatigue and time by instructing patients to sit on a bicycle seat with specially designed dilators to allow for progressive dilation by the weight of the patient's trunk. Ingram applied his technique both as a primary approach in some patients and as a secondary approach following neovaginal contracture after surgery. He reported neovaginal depths of 10 cm within 4–6 months, but it was unclear exactly what percentage of patients actually achieved this result.[44] In a larger series of patients with Müllerian agenesis treated with the Ingram method, functional success, as defined by satisfactory intercourse and acceptance of the largest dilator without discomfort, was reported in 34/37 patients (91.9%), although the series did not include younger patients (<18 years) and the mean time to achieve a functional neovagina was almost 12 months.[45]

There are advantages of this approach, including its noninvasive nature, low complication rate, preservation of native vaginal tissue, and lack of hospitalization. A longer starting vaginal length is advantageous. Another area in which the dilation method has been employed is contracture following a surgically created neovagina.[44] However, this seems to be much more successful when employed early (<6 months) following the operation. The main disadvantage to dilation techniques has been patient noncompliance, secondary to the time and persistent discomfort required to create a functional neovagina. Vaginal dilation can play an important role in the highly motivated patient who wishes to avoid surgery.

For patients with a simple vaginal dimple, a laparoscopic variation of the Vecchietti procedure may produce a neovagina. An acrylic mold with attached tension threads is placed at the dimple, with the threads passed under

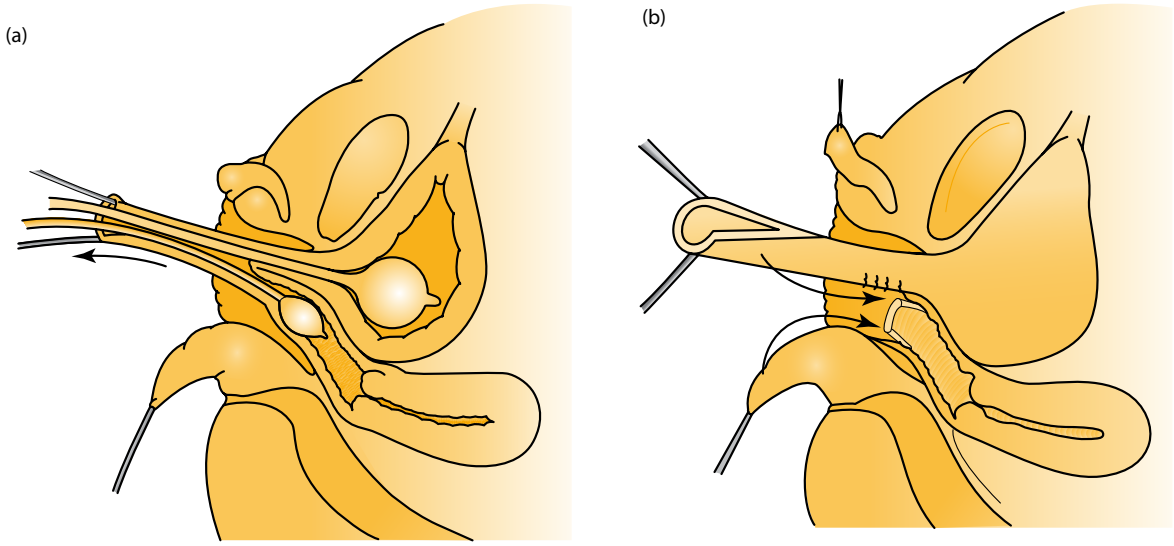

FIGURE 72.13 Options with total urogenital mobilization. (a) After adequate mobilization, the confluence may be advanced to the perineum. (b) Alternatively, mobilization allows good exposure for separation of the vagina and urethra. Anterior and posterior flaps may be used for vaginoplasty after releasing the urethra and vagina in the cephalad direction.

laparoscopic visualization through the abdominal cavity to a traction device on the abdominal wall. Increasing tension from the device is exerted daily over 1 week's time. The increase in tension is often painful, and vaginal dilation is necessary after removal of the mold to maintain vaginal length.[46]

Grafts

The use of split- or full-thickness skin grafts remains an option for vaginal replacement. McIndoe and Banister described the use of split-thickness skin grafts taken from the thigh and conformed to a cylindrical stent (Figure 72.14).[47] Space is created between the urethra and rectum in which the dermal surface of the skin graft is secured. The vaginal stent is left in place to be removed after a period of 7–10 days. A period of weeks to months of daily vaginal dilation is usually required to maintain patency and prevent vaginal stenosis. Full-thickness skin grafts have less reliable ingrowth of blood supply but contract less once in place and vascularized. Both skin grafts leave an obvious cosmetic mark at the donor site.

Buccal mucosa has been used for decades as a reliable substitution for urethra. Buccal mucosa is readily available and accessible, has mucosa-like characteristics, and acquires neovascularity quite easily and reliably if placed in an appropriate environment.[48] These grafts often show eventual squamous transformation when biopsied. The first reported series using buccal mucosa as a primary neovagina was in 2001.[49] There were no reported complications, and all patients reportedly had satisfactory experience with sexual intercourse. Since that time, other studies have reported successful outcomes using these grafts as a primary neovagina, while Oakes and colleagues reported the first use of buccal mucosa to augment a colonic neovagina following stricture formation.[48]

The obvious drawback to using buccal mucosa as a primary neovagina is the inability to achieve adequate-sized grafts.[48] The size of the graft itself can be augmented with small relaxing incisions prior to stretching over a mold, as in the Abbe–McIndoe technique. The ideal mold is 12 cm in length and 2 cm in width. Although a vaginal depth of 8 cm was reported in two series, long-term follow-up and validated sexual satisfaction questionnaires are lacking to conclude that this technique is superior to any of those previously mentioned.[49,50] These patients may also require prolonged postoperative dilation to maintain adequate neovaginal patency.[49,50] Zhao et al. were able to expand the size of buccal grafts by four- to sevenfold by mincing the tissue prior to implantation over a suitable mold.[51] Complications from these series were rare, but included inadvertent bladder and rectal injury, stricture, and bleeding.

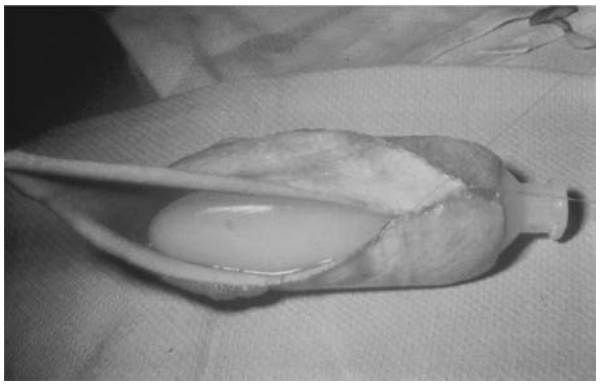

FIGURE 72.14 McIndoe skin vagina. A split-thickness skin graft is modeled over a stent.

The future of vaginal replacement may include grafting of engineered tissue. In 2007, Panici and colleagues cultured autologous vaginal epithelium that was incubated and grown to confluence in special medium. These cells were then mounted and embedded onto gauze that was placed within the host site over a mold. At 6 weeks, the patient was allowed to have intercourse. There were no reported complications.[52]

Flaps

Rotational flaps have been used to create a neovagina. Gracilis myocutaneous flaps,[53] pudendal thigh flaps,[54] labia minora flaps,[55] and flaps raised after tissue expansion have been described.[56] Unfortunately, patients with skin grafts or flaps for vaginal replacement may have problems with lubrication, graft contracture, or dyspareunia, and a need for chronic vaginal dilation.[57] Peritoneum from the pelvic sidewalls and pouch of Douglas can be mobilized laparoscopically and rotated to line a neovaginal space in a modification of the Davydov procedure.[58,59] Vaginal dilation is used after early removal of a mold. Sexual intercourse was successful for 25 of 28 women in a recent series, with vaginal dryness and discomfort a source of difficulty in some.[59]

Bowel Substitution

Advantages of the bowel vaginoplasty include natural lubrication from the intestinal segment, less problems with dyspareunia, and infrequent contracture or stenosis, usually without any need for routine vaginal dilation.[60–62] The sigmoid colon is generally preferred for vaginoplasty because of its proximity and ease of mobilization. In addition, the bowel segment does not need to be reconfigured. A segment of ileum, if more mobile, may also be useful but may require folding in an older patient. Patients may experience malodorous discharge after vaginoplasty, and stenosis may occur at the anastomosis site.

The patient is placed in a modified, low lithotomy position with careful support of the lower extremities to avoid neuropraxia. This position allows for a simultaneous abdominal and perineal approach by two surgeons. Through a low Pfannenstiel incision, the sigmoid is identified and evaluated for mobility. An 8–12 cm segment of sigmoid colon is identified and isolated with a window in the mesocolon at either end (Figure 72.15). A short segment is utilized because redundancy in length often results in eventual prolapse at the perineum. Bowel continuity may be reestablished with a stapled or hand-sewn anastomosis. Simultaneously, a second surgeon may perform perineal dissection by developing space between the bladder and rectum to the level of the peritoneal reflection in the cul-de-sac. Palpation of a catheter in the urethra aids

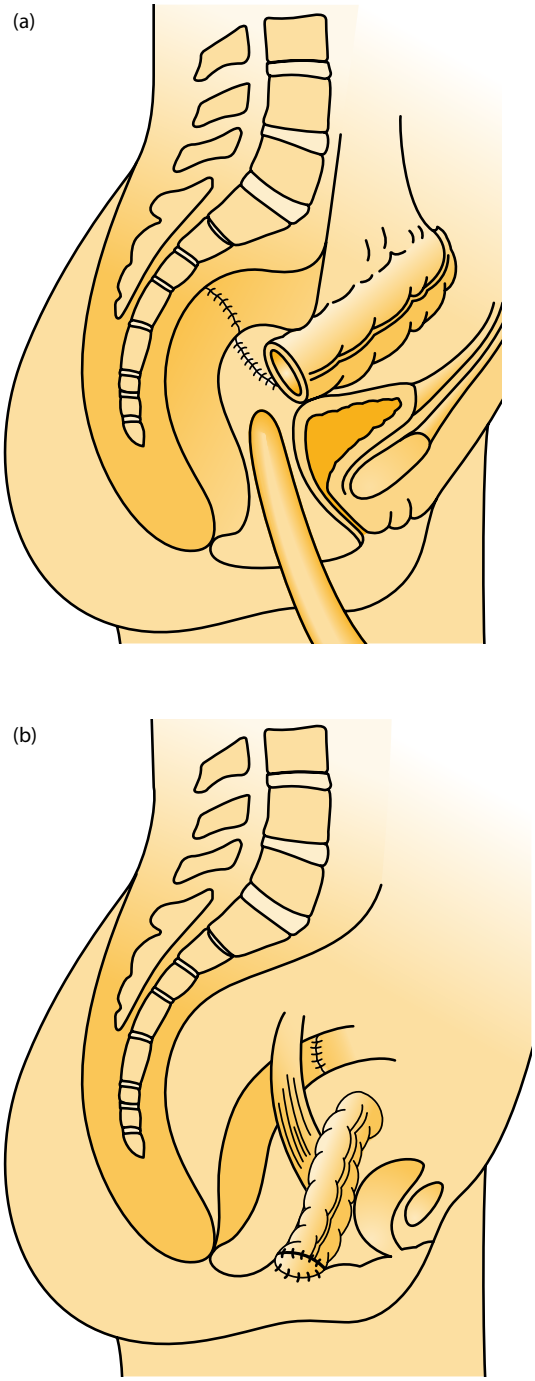

FIGURE 72.15 Sigmoid vaginal replacement. (a) A short segment of colon is isolated and space is created from below. (b) The bowel vagina is secured in place.

in identification of the proper plane. The peritoneum is incised from above and an adequate space created bluntly using a finger initially and then larger dilators. Care must be taken that the space is adequate along the entire length, particularly at the level of the pelvic floor. If an ileal segment is to be used, it is generally opened on its antimesenteric border and folded into a U configuration. Either segment of bowel is checked for viability. Very minimal tension at the distal end of the segment reaching to the perineum may not be problematic and may, in fact, help avoid future prolapse. Extreme tension on the mesentery of the bowel segment should be avoided whether using ileum or sigmoid colon. If such tension exists, creation of larger windows in the mesentery may be helpful, although careful identification of mesenteric vessels is critical. Serial transverse myotomies in the isolated sigmoid colon segment may also aid in lengthening of the segment. An inverted U-shaped perineal flap is often used to avoid the appearance of circumferential bowel mucosa at the introitus. The mobilized bowel segment is approximated to the perineal skin, the skin flaps, or a remnant of the native vagina with absorbable suture. The neovagina is packed with antibiotic-soaked gauze, which is removed after several days of healing. Irrigation of the bowel segment to avoid accumulation of excess mucus is then begun.

Other Procedures

Gonadectomy

A thorough chromosome evaluation is mandatory at the time of initial diagnosis in children with ambiguous genitalia. The presence of all or part of the Y chromosome in patients with disorders of gonadal differentiation may place them at increased risk for development of gonadoblastomas and other germ cell tumors.[63,64] Bilateral gonadectomies in such patients have been typically performed in the first several years of life; however, no consensus exists in regard to the optimal timing.

Gonadectomies are also performed in children with severe feminizing male pseudohermaphroditism who have undergone gender conversion. Laparoscopic excision may minimize morbidity and improve the cosmetic result; it also allows for therapeutic visualization of the abdomen, pelvis, and accessory sex organs. Longitudinal biopsy of the gonads may be appropriate in some patients for diagnosis or prior to excision.

Reconstruction for Male Pseudohermaphroditism

Male pseudohermaphroditism occurs when there is impaired genital differentiation of an XY male with developed testes and may result in a wide range of male and female phenotypes. Treatment of these children must be individualized, and appropriate surgical intervention may include relatively minor hypospadias repair, orchidopexy, or major genital reconstruction, including gender conversion. A detailed discussion of the treatment of these patients is found in Chapter 57.

RESULTS OF RECONSTRUCTION

Quality reviews documenting long-term results following feminizing genitoplasty or vaginoplasty in the setting of a urogenital sinus are lacking, particularly any with careful consideration to the initial anatomy or the surgical technique employed. Clitoral nerve conduction studies have identified preservation following clitoral reduction techniques and are encouraging in regards to ultimate clitoral

function.[65] Work evaluating orgasm and sexual satisfaction following such reconstruction is rudimentary at best.

More studies have evaluated the vagina after reconstruction in terms of more obvious complications, such as vaginal stenosis or urethrovaginal fistula. Studies evaluating the ability of the vagina to accommodate sexual intercourse after such reconstruction have provided sobering results. Jones and colleagues have noted that 30% of patients required surgical revision after initial vaginoplasty in order to achieve satisfactory intercourse,[66] and Azziz et al. reported satisfactory coitus in only 62% of patients 20 years following vaginal reconstruction in patients with CAH.[67] Many of those patients, however, had required secondary or tertiary procedures to correct stenosis at the introitus.

Early vaginoplasty may be a factor in the development of vaginal stenosis. Sotiropoulos et al. noted that all their patients operated on in the prepubertal period required revision of their introitus at a later date.[68] Bailez and colleagues, as well as Azziz, noted more revisions among children in whom vaginoplasty was performed prior to 1 year of age.[14,67] These older series included a wide range of patients with variability in the severity of the initial anomaly or even in the surgical techniques that were employed in their repair. It is possible that newer techniques for exposure, tissue handling, and use of flaps for vaginal reconstruction may change the surgical outcomes for the better; however, only long-term follow-up will determine if that is indeed the case. Careful attention must also be applied to define the severity of vaginal stenosis after reconstruction. Many stenoses may be minor and only result in the necessity for a minor revision, usually involving modified Z-plasty at the level of the narrowing. Such secondary procedures are certainly less troublesome than major rotational flaps that might be required for severe, extensive stenosis. The difference between the two has not always been well indicated in historic series.

The role of routine vaginal dilation in an attempt to avoid vaginal stenosis remains unclear. Routine dilation or calibration may help some patients avoid stenosis if done regularly, particularly patients destined to develop minor stenosis. It is less likely that routine dilation will avoid problems in patients headed for extensive fibrosis and stenosis. It is quite possible that long-term vaginal dilation or calibration may cause some psychological trauma for the patient or parent. Proponents of delayed vaginal reconstruction would suggest that the need for dilation or secondary surgical revision demonstrates the advantage of later reconstruction. It is clear that vaginoplasty, particularly for a patient with a moderate- or high-confluence urogenital sinus, is a major surgical procedure in an older patient. Such a procedure may likewise have a profound psychological impact on the patient and still carry risk for stenosis or other complications.

Urethrovaginal fistula can occur following reconstruction of the urogenital sinus, but fortunately is much less common than vaginal stenosis. Careful, yet aggressive, separation of the vagina and urethra allows adequate reconstruction of both structures and interposition of layers of tissue in between in order to minimize the risk of fistula. The most likely place to develop such fistula is the area of the initial confluence. Modern techniques that improve exposure and use more effective flaps for vaginoplasty should lower the risk of fistula formation. Total urogenital mobilization without separation of the proximal urethra from the vagina should carry virtually no risk for the problem.[38]

Despite the fact that modern techniques of clitoral reduction preserve nerve conduction following surgery, this finding may not equate to normal sensation or the ability to achieve orgasm, and further studies with self-reported validated questionnaires are warranted.[69–71] Pregnancy is possible in patients who have undergone vaginoplasty, and vaginal delivery can be safely recommended for those patients who undergo flap vaginoplasty and even total urogenital mobilization. However, pregnant women who undergo complex vaginoplasty with distal flaps are likely best served with an elective cesarean section.[72]

CONTROVERSY

Historically, the decision of gender assignment has been made shortly after birth by the parents in consultation with a multispecialty team. This choice involves many factors and includes genotypic sex and the functional potential of gonadal tissue, reproductive tracts, and the external genitalia. Such a scheme is still utilized in most centers. Sex assignment in infancy has been advocated by many, as it allows for early and consistent gender-specific social interactions throughout childhood. Support for this school of thought came from the observations and work of Money and investigators.[17,73–75] Partially driven by older patients unhappy with their sexual development, some of the lay and medical community have more recently questioned the timing and need for reconstructive surgery. Proponents of waiting and allowing for full participation in such decisions by the patient at a later age have appeared and gained support.[76,77] A few authors have called for a moratorium on genital reconstructive surgery until these concerns can be appropriately addressed.

It is beyond the scope of this chapter to address the moral, ethical, and gender identity issues involved with female genital surgery. It is important to note that while no universal practice policy has gained acceptance, it is incumbent upon the surgeon interested in such problems to be well aware of these issues and discuss them openly with patients and parents. Well-planned, long-term outcome studies are needed to address these problems and should lead to further refinement in the timing and techniques of genital reconstruction.

CONCLUSIONS

Significant strides have been achieved in surgical outcomes of patients with urogenital sinus abnormalities and intersex states. Evaluation of previous techniques, along with an improved understanding of genital anatomy and greater sensitivity to the complex nature of genital innervation, has led to improvements in terms of both cosmesis and, perhaps, function. Although complications, the most common being vaginal stenosis, may still occur following

female genital reconstruction, the ultimate expectation for the patient and family should be normal or nearly normal-appearing and functioning genitalia. Even when such a result is achieved, the underlying problem and process of reconstruction often have a profound psychological impact on the patient, particularly in terms of sexual identity. It remains to be determined how the best functional end point can be achieved for the patient with the least morbidity in that regard.

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CHAPTER 73

Hypospadias

Warren T. Snodgrass and Nicol Corbin Bush

INTRODUCTION

With a prevalence of 1:200 males, hypospadias is one of the most common congenital anomalies. Each year, 10,000 boys are born with the condition in the United States, or an average of 27 every day. In contrast, there are 16 new infants with Down's syndrome, 12 with cleft lip, and only 4 with spina bifida born daily.[1]

Nevertheless, hypospadias is uncommon, and proximal hypospadias is a rare condition, with only 1000 new cases each year. After reviewing case logs submitted by pediatric urologists applying for specialty certification, the American Board of Urology reported that the median number of distal repairs done annually is only 12, and only 2 for proximal hypospadias.[2]

Given that hypospadias surgery, even for distal defects, is complex, and that a growing body of literature shows that outcomes from complex operations are best from surgeons who perform them frequently, it is not surprising that many patients develop complications after their repairs. Although surgeons may claim 95% success for distal repairs, the Dutch Hypospadias Study prospectively recorded results from surgeons throughout the country and found that complications ranged from 4% to as high as 63%, and averaged 16%.[3] Outcomes from proximal hypospadias surgery are even worse, with several U.S. centers recently reporting complications in 55% to nearly 80% of cases.[4–6]

No other surgery done by pediatric urologists harms more patients than hypospadias repair.

Furthermore, numerous studies regarding hypospadias reoperations agree that complications are higher than in primary repairs. We found that even the first reoperation had twice the risk for additional urethroplasty complications, and after three failed repairs the risk was 40%.[7] Even surgery for distal hypospadias sometimes results in a hypospadias cripple.[8]

These observations emphasize that there is no "minor" hypospadias, and that it is important that repairs be performed optimally the first time. To that end, this chapter presents a limited surgical algorithm and highlights the key steps of each procedure. By using fewer techniques and gaining expertise in their key steps, surgeons can improve their results and increase the likelihood for boys to achieve a normal penis.

PREOPERATIVE ASSESSMENT

Isolated versus Syndromic Hypospadias

Approximately 90% of hypospadias cases are isolated penile defects. Syndromic hypospadias is suspected when there are additional nongenital anomalies, especially dysmorphic facies and anorectal malformation.

Imaging

Renal abnormalities have been reported in approximately 20% of hypospadias patients, mostly ureteral duplications, malrotations, or minor hydronephrosis not requiring intervention. Vesicoureteral reflux has been found in approximately 10% of patients studied with voiding cystourethrography (VCUG). There is no correlation in reported series between the severity of hypospadias and these findings.[9,10] We do not image boys with isolated, that is, nonsyndromic, hypospadias regardless of its severity.

Imaging may also demonstrate an enlarged utricle in boys with proximal hypospadias. However, this information is of limited value, as nearly all utricles are asymptomatic. Those encountered intraoperatively because of difficulty passing a catheter into the bladder can be bypassed using a Coude-tipped catheter or a guidewire with or without urethroscopy.

Disorders of Sexual Differentiation

By definition, hypospadias and intersex are separate conditions. While some patients with a diagnosis of disorder of sexual differentiation (DSD) have hypospadias, few patients with hypospadias also have DSD, and even fewer question their male gender identity. No published series reports the results of evaluation in consecutive patients with hypospadias to determine the prevalence of DSD. Rather, testing has been selective, most often for the combination of hypospadias with an undescended testicle. Karyotyping in this situation has found chromosomal anomalies in <33% of those studied.[11–13] However, a normal karyotype does not exclude DSD, as occasionally an ovatestis is encountered during harvesting of the tunica vaginalis for a coverage flap in proximal repairs, despite both testes being descended.

It is important that physicians avoid casual use of such terms as *ambiguous genitalia* and *intersex* when discussing findings in a newborn with apparent hypospadias. First, palpable gonads essentially exclude ambiguous genitalia despite even perineal hypospadias. Second, caregivers are frequently already anxious about a diagnosis of hypospadias, which most have never heard of, and the Internet search that inevitably follows these words creates even greater anxiety, including worry about whether their son is actually a boy. The diagnosis of DSD associated with hypospadias almost never implies future gender identity confusion.

Hormonal Therapy

Preoperative hormonal therapy has been advocated to increase penile size and vascularity to improve outcomes of repairs, especially for proximal hypospadias. Numerous studies show that stimulation can increase penile length and glans circumference, and one study reported an increase in prepucial vascular density.[14] However, indications for treatment are ill-defined, dosing regimens are empiric, end points for therapy are rarely stated, and no study demonstrates reduced complications for proximal repairs after stimulation.

We realized that glans dehiscence occurred more often following proximal tubularized incised plate (TIP) repairs than distal TIP repairs done by the same surgeon using the same sutures and glansplasty technique.[15] Suspecting that a smaller glans size in proximal hypospadias potentially explained these findings, we next measured the glans diameter in consecutive boys undergoing distal and proximal repairs, and in newborns undergoing office circumcision.[16] The average width in those with proximal hypospadias was significantly smaller than that measured in other boys (12.9 mm vs. 14.3 and 14.8 mm in distal hypospadias and normal boys, respectively).

Next, we began testosterone injections in boys with a glans width of $\leq$13 mm, with the goal to increase it to $\geq$14 mm. We found that our use of testosterone doubled using the objective criteria of a measured glans width compared with earlier subjective use for a small-appearing glans. In addition, we found that the standard recommended regiment of two or three injections of 2 mg/kg testosterone cypionate failed to achieve the desired increased width in 57% of patients, indicating androgen resistance.[17] Finally, successful enlargement of the glans did not reduce urethroplasty complications after surgery done approximately 6 weeks later, which remained three times more likely than in boys with a similar glans width without stimulation. In fact, the statistical model found testosterone to be a risk factor for complications.[18] Therefore, we stopped using testosterone stimulation.

Potential side effects of hormonal stimulation include accelerated bone aging and pubic hair. Two studies regarding bone age reached different conclusions.[19,20] Pubic hair growth was reported in 0 of 25, 2 of 25, and 5 of 21 boys receiving various regimens of topical or injected testosterone.[19,21] We have evaluated several boys who grew pubic hair after stimulation (Figure 73.1).

FIGURE 73.1 Pubic hair growth following testosterone treatment. Six-year-old treated with testosterone after failed distal hypospadias repair. The hair has persisted during 4 years' follow-up.

It is also important to emphasize that few boys with proximal hypospadias have micropenis. That diagnosis requires a stretched penile length of $<$2 standard deviations (SD) below the mean in a patient with normal internal and external male genitalia.[22] For infants 6–12 months, a micropenis is $\leq$2.3 cm. Obviously, it is difficult to accurately determine penile length in boys with ventral curvature (VC). While boys with proximal hypospadias may have penile measurements below the mean, few are less than 2 SD, which means that their smaller penis sizes are nevertheless within the normal range.

Imprecise use of the term *micropenis* by physicians to caregivers of boys with hypospadias can cause unnecessary anxiety regarding future sexual potential.

Determining the Need for Repair

The goal of hypospadias repair is to create a normal penis, meaning a straight penis with the opening in the correct location at the tip. The normal glans encloses the urethra, and the distance from the lower lip of the meatus to the corona in normal boys is a mean of 4.7 mm and a minimum of 2.4 mm[23] (Figure 73.2).

The normal urine stream is straight and compact, that is, does not spray. When the meatus is not enclosed by the glans for at least 2.5 mm, the likelihood the boy or man will experience deflection and/or spraying increases. Parents usually do not notice these abnormalities in their infant sons, which become more apparent when the patient achieves a sufficient height after toilet training that the penis is not inside the toilet while urinating.

Even teens and adults with uncorrected hypospadias who stand to void without difficulties may experience body image concerns regarding their penis.[24] Those who

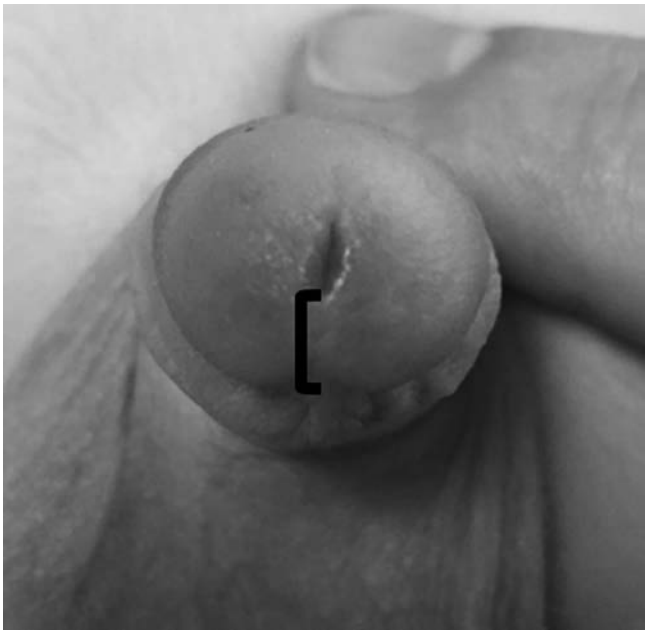


FIGURE 73.2 Normal penis. The bar shows the normal distance that the distal urethra is enclosed by the glans wings, which is >2.5 mm, averaging 4.7 mm. Deviation from normal in distal hypospadias increases the potential for urine spraying.

elect surgery commonly say they wish to "be whole," and report they had anxiety around peers and new sexual partners.

Hypospadias repair is not cosmetic surgery. The American Society of Plastic Surgeons defines *cosmetic surgery* as the enhancement of normal body parts, whereas *reconstructive surgery* includes repair of congenital defects.[25] This distinction is important, given that many parents express concern about performing cosmetic surgery on their son's genitalia, but are reassured when informed that the operation is reconstructive to achieve normal appearance and function.

No study describes functional and psychologic outcomes in an unselected cohort of teens and young adults with uncorrected hypospadias. Therefore, the number of those who will experience voiding disturbance and/or emotional distress is not known. However, a survey of patients with uncorrected hypospadias who presented to pediatric urologists found that 33% were dissatisfied with their penile appearance, 41% were concerned about what others would think about their appearance, and 54% were dissatisfied with their voiding, with 37% describing spraying or deviation of the stream. Fifty percent of these patients held strong negative feelings about their penis body image.[24]

Informed consent regarding surgery for distal hypospadias best states that there is a risk for functional and aesthetic concerns in patients with abnormal anatomy, and accurately describes repair as reconstructive surgery.

Caregiver Guilt

The diagnosis of any birth defect can be devastating to parents, who then often experience stages of grief for the "loss" of the normal child they expected.[26] Mothers often feel guilty, believing something they did, or failed to do, during pregnancy caused the problem. Adding to these concerns are the isolation and shame of a defect involving the penis that neither they nor their family and friends have heard of. Parents have told us that they went through staged reconstruction of their son's proximal hypospadias without the support of extended family or friends because others did not know about hypospadias and they were too embarrassed to discuss a defect of the penis.

Parents also may describe frustration trying to learn more about hypospadias once they have been told the diagnosis. In their view, office consultations with surgeons may be too focused on arranging surgery, and not on discussing the reasons hypospadias occurs and its potential impact on future sexual activity and fertility. Most have researched the Internet and grown even more confused about these subjects. They have also been exposed to both professionals and activists claiming that surgery is cosmetic, repairs are not durable, and surgery on the penis reduces future pleasure by creating scars and decreasing sensation. If they have gotten second opinions, parents can be frustrated by the lack of consensus regarding treatment.

Simply acknowledging these possibilities during the consultation can indicate both awareness of their concerns and an interest by the urologist in more than the surgical aspects of the condition. More research into parenteral reactions to the diagnosis of hypospadias is needed. Recommendations to appropriate mental health providers, such as licensed therapists to help patients and families deal with anxiety and stress related to hypospadias, should be provided.

Timing of Surgery

We published that surgery for distal hypospadias repair can be safely accomplished as early as 3 months of age for full-term and healthy infants, in facilities with pediatric anesthesia and nursing.[27] Infants with proximal hypospadias are more likely to be born prematurely, or with intrauterine growth retardation, which delays repair until the child is gaining weight and can undergo outpatient surgery. We wait until at least 6 months of age before operating for proximal hypospadias to also allow for maximum penile growth from postnatal mini-puberty.

There is belief that surgical outcomes are better in younger patients, but several retrospective case series reported conflicting results, with increasing complications after 6 months, 1.5 years, or 4 years of age.[28–30] Our data, collected prospectively in consecutive patients undergoing TIP repair, found age was not an independent risk factor for urethroplasty complications.[27]

Another question arises when there is both hypospadias and an undescended testicle, regarding surgical management. In distal cases, orchiopexy and hypospadias repair can be done simultaneously, or in a staged fashion according to surgeon preference. However, in proximal cases we first correct the hypospadias to preserve tunica vaginalis to cover the neourethra, and to correct penoscrotal transposition before anchoring the testes.

INTRAOPERATIVE MANAGEMENT

Nerve Blocks

Regional nerve blocks reduce the intraoperative level of general anesthesia, and initial postsurgical pain. Caudal blocks, penile nerve blocks, and pudendal nerve blocks are options, with the decision often made according to the preference of the anesthesiologist. A potential disadvantage of dorsal penile nerve blocks is migration of medication into the penile shaft, distorting the surgical field. Dissection along the ventral midline near the glans can also provoke discomfort if a supplemental injection is not done in the perineum or scrotum.[31] A potential disadvantage of caudal blocks is increased likelihood for intraoperative penile engorgement. No appropriately designed randomized controlled trial has been published to date that specifically investigates if complication rates vary by type of regional block.

Preoperative Antibiotics

There are no data supporting preoperative antibiotic administration for hypospadias repair. Similarly, there are no reports regarding wound infection following hypospadias surgery to determine the incidence, means for diagnosis, or organisms encountered.

We do not use antibiotic prophylaxis, except for a single dose of cefazolin before oral graft harvest.

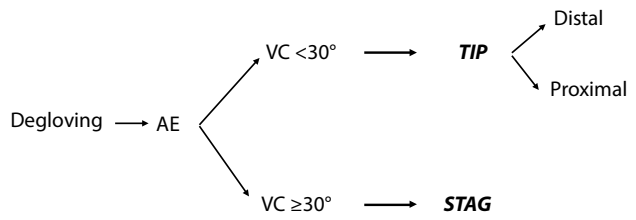
Decision Making for Primary Repairs

We correct all hypospadias using two surgical techniques: TIP repair and staged tubularized autograft (STAG) repair (Figure 73.3). These methods are similar in that TIP involves tubularization of the urethral plate, while STAG is tubularization of a neourethral plate of oral or prepucial autograft.

Traditionally, decision making among a variety of available techniques was made by the surgeon's assessment of the specific anatomy encountered, meatal location (distal or proximal), and the surgeon's preference. However, characterization of the anatomy includes subjective impressions with significant interobserver variation.[32] This introduces selection bias, which results in different recommendations for a given patient, and difficulties in comparing outcomes of various series.

Decision making for TIP versus STAG depends on the extent of VC determined after degloving and release of ventral penile dartos and any scrotal dartos extending up the penile shaft. Patients with a VC of <30° undergo TIP, while those with a VC of >30° have STAG repair, regardless of meatal location.

While we do not perform flap repairs, some, especially the onlay prepucial flap, remain in use as an alternative to proximal TIP.



AE: artificial erection

FIGURE 73.3 Algorithm for primary hypospadias repair. The surgical algorithm is based on the extent of associated VC, rather than primarily on meatal location. While there are other options, this algorithm covers all primary hypospadias.

SURGICAL REPAIR

Straightening Ventral Curvature

Ventral bending of the penis relates to three factors: short ventral shaft skin, a short urethral plate, and short ventral corpora ("corporal disproportion").

Preoperative assessment frequently suggests VC, even in patients with distal hypospadias, and caregivers are often informed that their son has "hypospadias with chordee." Much of this apparent bending resolves spontaneously while degloving the penis, commonly leaving a gap between the skin and the glans. In most distal hypospadias, degloving corrects any VC, indicating the etiology was short ventral skin.

Artificial erection after degloving, including release of ventral penile and scrotal dartos attachments to the shaft, may demonstrate that the penis is straight, or that there is a curvature of <30° or ≥30°. Measurement of bending should be done objectively, using a goniometer (Figure 73.4).

A VC of <30° is straightened by dorsal plication (Figure 73.5). Buck's fascia is opened longitudinally in the dorsal midline at the point opposite the greatest curvature. A single 5-0 polypropylene suture is placed into the tunica albuginea, burying the knot. The maximum distance traveled by the needle is approximately 4 mm. Adjacent dartos is then sutured over the plication to further conceal the knot. Repeat erection is done to confirm straightening.

Nesbit plication involves incision into the tunica albuginea, or removal of an oval of the tunica, before suturing. Traditionally, this was done bilaterally, lateral to the midline after elevating penile nerves. There are no data showing that this method is superior to the less invasive midline (Baskin) plication.

A VC of ≥30° should not be straightened by dorsal plications, because the straightening initially achieved may not be durable.[33–35] Rather, the next step is to transect the urethral plate at the corona and dissect it (including the wings of the corpus spongiosum) back to the meatus (Figure 73.6). We then continue this dissection proximally, releasing the formed urethra from the corpora to near the external sphincter (Figure 73.6). Any remaining dartos or corpus spongiosum ventrally is excised from the corporal surface. Then artificial erection is repeated. Correction of a VC, or its reduction to <30°, by this maneuver indicates that bending was largely due to a short urethral plate. A residual curvature of <30° is straightened by midline dorsal plication. A persistent curvature of ≥30° should not be

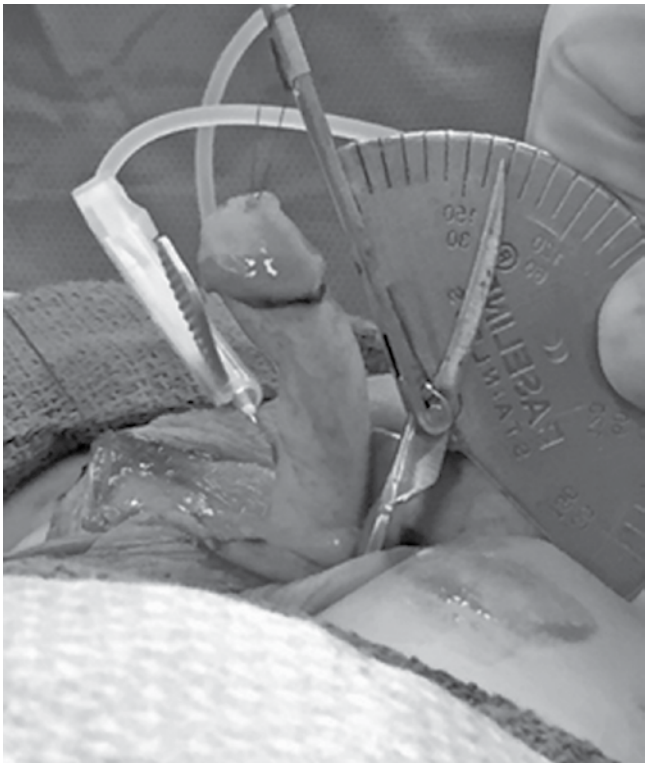


FIGURE 73.4 Measuring VC using a goniometer. This devise, used in hand surgery, makes determination of the degree of VC objective, and therefore more accurate. This patient has a 30° curvature, which is not visually impressive.

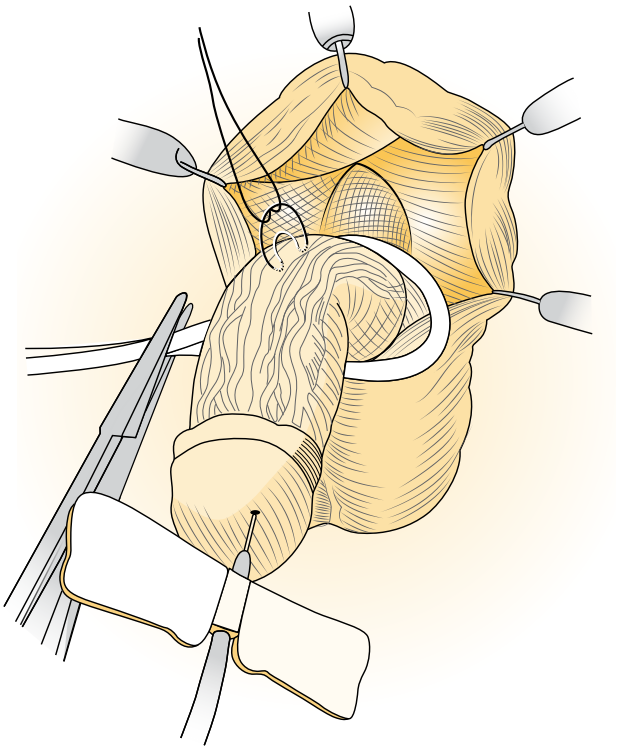


FIGURE 73.5 Midline dorsal plication.

straightened with plication alone due to the high recurrence rates of VC.

A persistent VC of ≥30° after dissection of the urethral plate and urethra off the corpora indicates short ventral corpora, which is corrected with ventral lengthening. We incise the ventral tunica albuginea in three locations, first through the area of maximum bending, and then 4 mm above and 4 mm below the first (Figure 73.6). These incisions are transverse, from approximately four to eight o'clock, extending just through the tunica. Artificial erection is repeated, now using a 21-gauge butterfly to achieve sufficient inflow, which should confirm straightening (Figure 73.6). Generally, there is a gain in length of 8–10 mm along the ventral surface of the penis after the three corporotomies. We do not place a corporal graft over the corporotomies, but we do additionally place a single midline dorsal plication to supplement the corporotomies.

Ventral lengthening has also been done by a single transverse corporotomy from three to nine o'clock, followed by a graft of dermis, or other materials, to cover

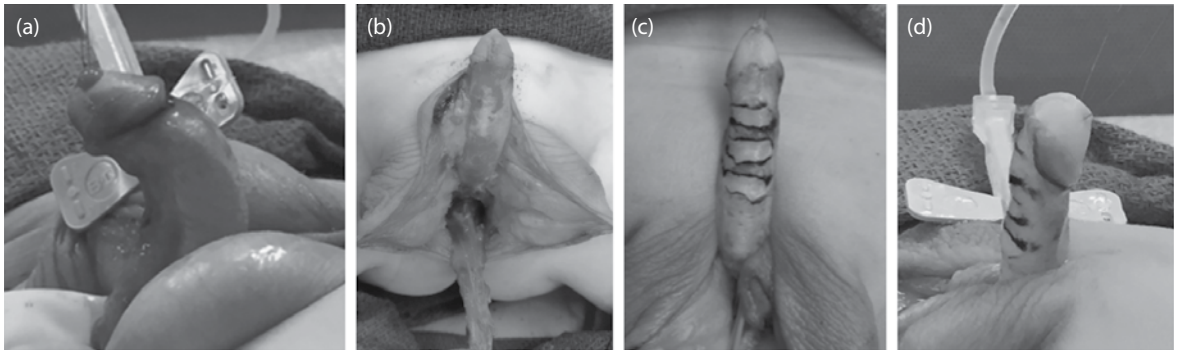


FIGURE 73.6 Straightening VC of >30°. (a) Artificial erection after degloving and dissection of ventral dartos and scrotal encroachments onto the penile shaft shows a persistent curvature of >30°. (b) The urethral plate was transected at the corona, and then dissected off the corpora to the intact urethra. Dissection continued proximally, mobilizing the urethral plate–urethra complex to near the external sphincter. Any remaining dartos and Buck's fascia was excised from the tunica albuginea of the ventral corpora. (c) Three transverse corporotomies have been made, extending just through the tunica albuginea from approximately four to eight o'clock. The first was made across the point of maximum bending, with the other two made 4 mm proximally and 4 mm distally. (d) Repeat artificial erection with a 21-gauge butterfly shows the penis to be straight.

the tunica defect. There are two disadvantages to this method. The most important is that it limits urethroplasty options to prepucial flaps, such as one-stage tubularized prepucial flaps or two-stage Byars prepucial flaps, both of which have been recently reported to have high complication rates.[4–6] In addition, there may be a greater risk for recurrent curvature when lengthening relies on a single, rather than multiple, relaxing incisions.

Most boys with distal hypospadias have no VC after degloving, and the remaining 10% have a VC of less than 30°.[36] The rare patient found to have a VC of ≥30° should be considered to have a proximal hypospadias variant. Certainly, the meatus will move proximally after the urethral plate is transected in this situation.

At least 50% of boys with proximal hypospadias have a VC of ≥30°.[35] Optimal management of this bending has been controversial. When Duckett observed the curvature persisted when the urethral plate was transected, he decided there was little benefit to that maneuver and instead advocated using multiple dorsal plications to make the penis straight. This decision reflected his increasing preference for onlay flap repair onto the urethral plate, versus the tubularized flap repair he used when the urethral plate was removed.[37]

In contrast, Bracka routinely excised the urethral plate, initially in all hypospadias repairs, because he performed two-stage graft procedures. He recommended that any persisting curvature be straightened by plications at the second stage.[38]

However, plications have been found less durable for straightening than ventral lengthening.[33,34] We have encountered a VC of ≥30° in 80% of patients evaluated for complications after primary proximal hypospadias repairs done elsewhere by pediatric urologists.[35] Not only do these boys have recurrent fistulas and wound dehiscences, presumably from tension on the urethroplasty from the curvature, but straightening requires excision of the neourethra and STAG repair using oral mucosa since the foreskin is no longer available. Often this is complicated by insufficient ventral penile skin related to the recurrent VC, which also complicates reoperation.

Inadequate straightening reflects not only earlier recommendations for plications, but also confusion regarding the etiologies of curvature. Because the term *chordee* mixes the three different causes of bending into a single description, it limits understanding of the condition and its best management. There is no chordee tissue, and bending is due to short ventral skin, a short urethral plate, or short ventral corpora.

Distal Hypospadias Repair

We repair all distal hypospadias by TIP. In the following description of the technique, key steps that impact outcomes are highlighted in bold type.

The glans width is determined using calipers (Figure 73.7), and a 5-0 polypropylene stay stitch is placed. An 8Fr sound is passed into the distal urethra, and if it appears "thin," indicating deficient spongiosum and dartos covering, the ventral incision is extended in a U shape proximally below the thin area. The two corners of the dorsal hood are lifted and lines for incision marked as shown (Figure 73.7).

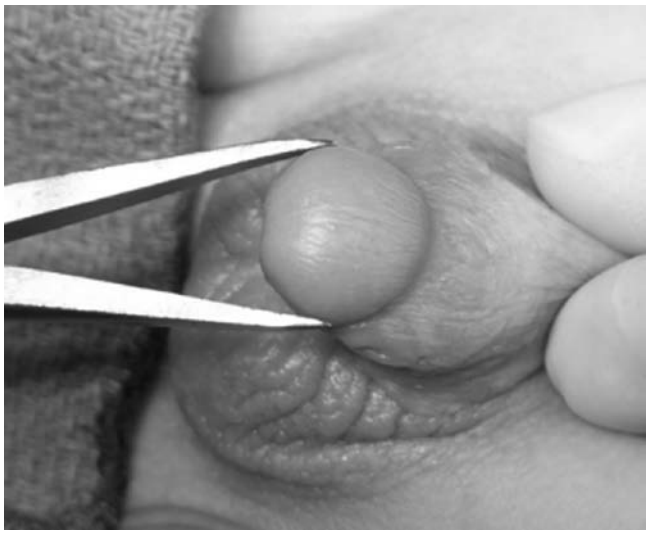


FIGURE 73.7 Measuring glans width. The width of the glans should be measured at the outset of every repair using calipers.

The oblique dorsal extensions allow inner prepucial skin to rotate ventrally and provide a uniform "collar" of inner prepuce, mimicking circumcision in normal boys.

The penis is degloved. The correct plane for ventral dissection is immediately under the skin, preserving the ventral dartos to subsequently create a flap to cover the neourethra. The ventral skin is released to the penoscrotal junction. Dorsal dissection is done along Buck's fascia to near the penopubic junction. Artificial erection is done, with a VC of <30° straightened by midline dorsal plication as described above.

A tourniquet is wrapped around the penile base, either before or after artificial erection. Next, the urethral plate–glans junction is marked, creating mirror image lines that run along the contour of the glans wings and end lateral to the meatus on each side (Figure 73.8a). We make these incisions extending distally 1 mm beyond the urethral plate, to approximate the glans wings at the correct location for the neomeatus. Epinephrine (1:100,000) is injected under the incision line. We use both a tourniquet and injected diluted epinephrine to reduce bleeding during glans wings dissection.

A 69 Beaver knife is used to superficially incise the marked lines, and then tenotomy scissors continue dissection deeper to the surface of the corporal bodies. The correct plane leaves the glans wings sufficiently thick for their later suture approximation, without creating holes in the urethral plate medially. Once the corporal surface is identified, the glans wings are mobilized laterally to three and nine o'clock (Figure 73.8b).

Based on our observation that urethroplasty complications increase with a decreasing glans width of <14 mm, further mobilization of the glans wings is done in those cases. After standard dissection to three and nine o'clock, "extended" dissection is done distally along the surface of the corpora for approximately 4 mm to reduce tension on subsequent glans wings approximation (Figure 73.9).

Occasionally, a hole is made in the side of the urethral plate as the glans wings are created. We loosely

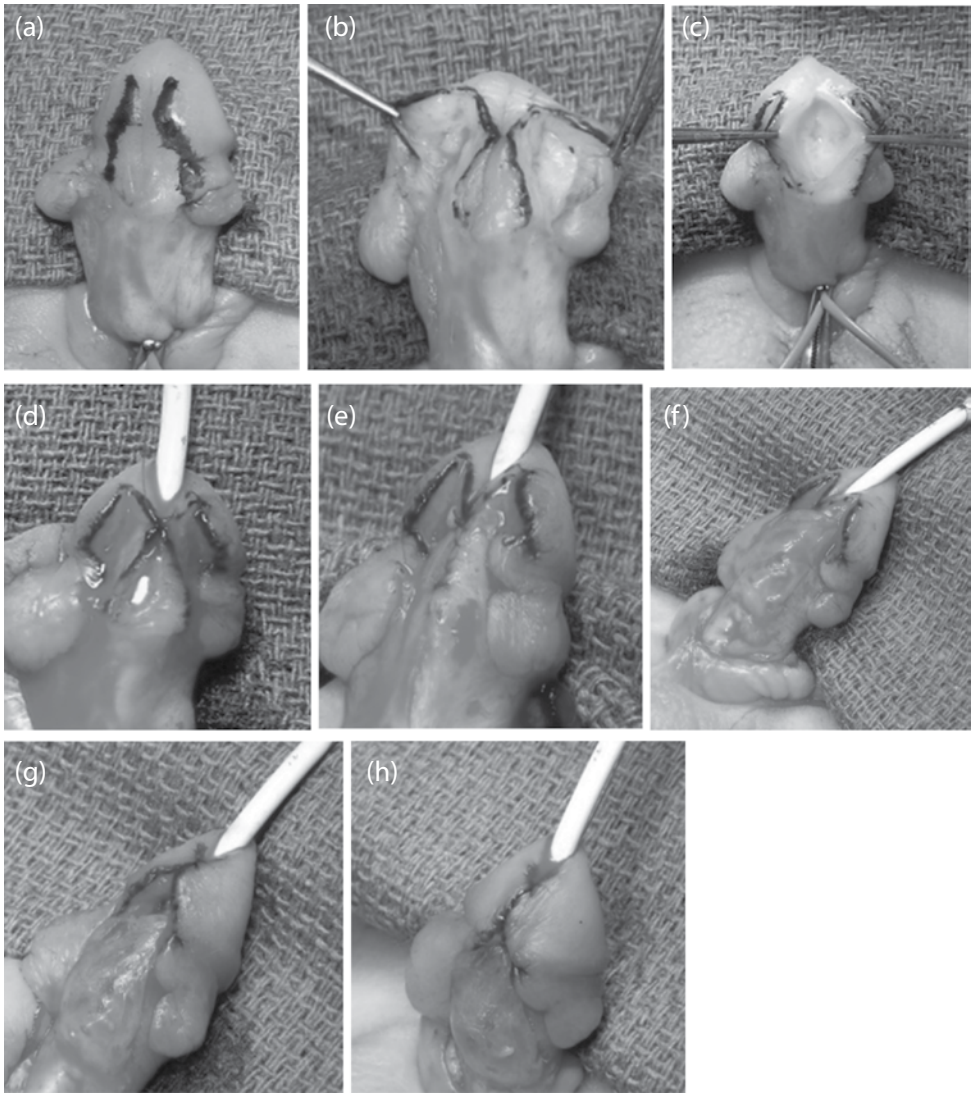


FIGURE 73.8 Key steps in distal TIP repair. (a) After degloving, lines mark the visible junction of the glans wings to the urethral plate. (b) Glans wings have been dissected from the corpora cavernosa laterally to three and nine o'clock. (c) The urethral plate has been deeply incised to the tunica albuginea of the corpora cavernosa. The incision extends from within the meatus to the end of the plate distally. *Urethral plate incision should always be done to this extent*. (d and e) The first stitch for tubularizing the urethral plate is placed at the midpoint of the glans wings. Note the wide oval opening. Placing the most distal stitch at this point avoids iatrogenic meatal stenosis. (f) A dartos flap covers the entire neourethra. (g) The first glansplasty stitch is also placed at the midglans, and the glans wings are approximated together but *not* sewn to the opening in the urethral plate. This stitch establishes the neomeatus. (h) Glansplasty is completed with a total of three interrupted subepithelial stitches. Note the distance from the lip of the neomeatus to the corona, which averages 4 mm in TIP and STAG repairs—well within the normal range.

close the defect using interrupted 9-0 polyglactin, realizing it will later be covered by the ipsilateral wing during glansplasty.

Next, the urethral plate is incised. The edges are held on either side with 0.5 mm Castro–Viejo forceps, gently stretching laterally to delineate the midline. The plate is incised from within the meatus to its tip, and from the epithelial surface deeply to the tunic of the corporal bodies underneath (Figure 73.8c). This key step is done in every case, and failure to incise the plate down to the corpora is a major technical error, increasing risk for complications.

A 6 Fr stent is passed into the bladder and tied to the glans traction suture. Its purpose is only to divert urine, and it is specifically not used to size or mold the neourethra.

Urethral plate tubularization begins distally at the midpoint of the glans wings (Figure 73.8d and e). Tubularization too far distally is also a major technical error.

The first stitch is through epithelium, and then the remainder of the closure is subepithelial, continuing proximally where a second knot is tied. Then the same suture returns a second subepithelial layer distally. We use 7-0 polyglactin on a TG 130 needle, because this ophthalmic needle is smaller than needles available on monofilament sutures. Failure to perform two-layer closure during urethroplasty increases the risk for complications and is another potential technical error.

FIGURE 73.9 Extended glans wings dissection for a glans width of <14 mm.

Next, a dartos flap is created and used to cover the entire neourethra (Figure 73.8f). The lack of a coverage layer increases the risk for fistulas.

If ventral degloving was done close to the shaft skin, sufficient dartos for this flap remains without having to reset traction to harvest it dorsally. However, a dorsal dartos flap can also be used, with care taken to avoid torsing the penis when it is transferred ventrally.

Glansplasty sutures the previously dissected glans wings together over the neourethra (Figure 73.8g and h). The glans is not directly sutured to the opening in the tubularized urethral plate. Most often, three interrupted subepithelial sutures complete the approximation, providing glans fusion that typically measures 4 mm.

We first place a 9-0 polyglactin stitch through the epithelium at approximately the midpoint of the glans wings to create the neomeatus. Then a subepithelial 6-0 polyglactin stitch on an S29 needle is placed immediately under the 9-0 suture, which is removed. The 9-0 stitch helps visualize the distal-most glans wings approximation before completing the glansplasty.

Then two more 6-0 polyglactin subepithelial stitches are placed, the second including a small bite of dartos to hold it in place, and the third approximating the coronal margin.

Mattress sutures should not be used for glansplasty, as they can result in suture marks or even deep cuts into the glans tissues (Figure 73.10).

Shaft skin from the area of the original meatus is next excised. Then the inner prepuce is joined in the midline using subepithelial 7-0 polyglactin. A 9-0 polyglactin can be placed through the glans epithelium just at or below the corona to close these skin edges, with little concern for later visible suture tracts due to the small size.

Next, the dorsal prepuce is cut down the middle to the lower edge of the inner prepucial collar and sutured there with 7-0 polyglactin. Ventral skin is closed into a median raphe, and finally, excess skin is excised to complete the circumcision. All skin edges are closed subepithelially to avoid suture tracts that can develop with epithelial sutures.

The catheter is removed in 5–7 days.

Prepucioplasty

Some parents prefer that the foreskin be reconstructed instead of hypospadias repair with circumcision. Given that nearly all published series report that urethroplasty and skin outcomes are the same for distal hypospadias repairs done with either circumcision or prepucioplasty, surgeons should follow caregiver wishes.[39] If a surgeon chooses not to do prepucioplasties, then it is most appropriate to refer interested families to others who will, rather than attempting to persuade them to accept circumcision. This is especially true in cultures where most boys and men are not circumcised, where those who are circumcised are considered by their peers to be different.

The two corners of the dorsal hood are identified and then held with 5-0 polypropylene stay stitches throughout

FIGURE 73.10 Glans injury from mattress sutures. Mattress sutures for glansplasty can cut through the glans wings, as seen in this case, and should not be used.

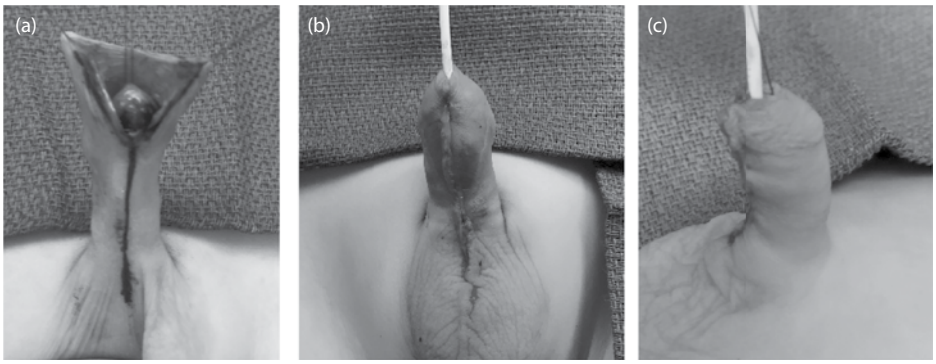


FIGURE 73.11 Prepucioplasty. (a) V or Y ventral skin incision. (b and c) Completed repair.

the operation (Figure 73.11a). A ventral V incision extends from the stay sutures to 2 mm below the meatus. This incision can be continued down the median raphe into a Y configuration, especially when minor scrotoplasty is needed to lower the scrotum. Degloving is confined to the ventral penile surface, but can extend as far proximally as desired, preserving the underlying dartos to create a coverage layer for the neourethra.

Should a VC of <30° be found, the dorsal midline can be approached for plication without degloving by dissecting the shaft skin around the dorsal surface of the penis while leaving the distal prepuce still attached.

Glans wings dissection, urethral plate incision, and tubularization, glansplasty, and dartos coverage of the urethra are done as described above, with the dorsal foreskin wings retracted down.

Then the inner prepuce is approximated using interrupted subepithelial 7-0 polyglactin. The foreskin stays are then pulled distally, and a second layer of sutures closes the dartos. Finally, the outer foreskin is sewn together, also using 7-0 polyglactin interrupted subepithelial stitches (Figure 73.11b and c).

Originally, we tested foreskin closure to enssure that it easily retracted and reduced over the glans, and repositioned the most distal stitches lower when it did not. However, we now place the distal stitches where needed to give the most normal cosmetic appearance and are not concerned if the skin retracts—since it does not usually retract in normal boys the age of those undergoing hypospadias repair. Although steroid cream can be applied to a reconstructed foreskin that does not retract, our experience is that no treatment is needed for the majority, as the skin will do so eventually. Parents are told that the glans may not be visualized for some time, even more than a year, after prepucioplasty. They are instructed to avoid forced manipulation of the foreskin for several months after surgery.

TIP versus G-TIP

A variation on TIP is the grafted-TIP (G-TIP) incision or repair. Proponents claim several potential advantages: making a flat plate suitable for tubularization, less likelihood for urethral scarring, and/or better distal location of the meatus. Typically, the graft has been taken from the foreskin otherwise being discarded during circumcision. An alternative donor site would be needed when families wanted prepucioplasty.

No study has shown either increased or reduced complications from G-TIP versus TIP. We believe any advantage comes from encouraging surgeons to make the TIP incision deeply, in this case to place the graft. Our data in consecutive TIP repairs consistently show that the neomeatus is normally positioned, with an average glans fusion length of 4 mm.

Urethral Plate Configuration

Some surgeons have expressed concerns that a "flat" plate should either have G-TIP or an alternative repair. Others worry about TIP when the urethral plate measures <8 mm.[40,41] We published outcomes from distal TIP that are the same regardless of whether the plate is flat, "deep" or in between.[42] We also found that the urethral plate measured less than 8 mm in 85% of consecutive patients, but width did not correlate with outcomes.[43]

Results

A systematic literature review that included 23 publications with 1872 distal TIP repairs reported 4% fistulas and 3% meatal stenosis.[44] A subsequent meta-analysis included 49 studies and 3621 distal TIP repairs, finding fistulas in 6%, meatal stenosis in 4%, and urethral strictures in 1%. The reoperation rate for complications was 4.5%.[45]

We tallied complications reported by publications from 1994 to 2009, finding that they ranged from 0% to 24%. Of the 35 articles, 25 had overall complication rates of <10%.[46]

We also published our series of distal repairs in consecutive patients, using no other surgical technique. Complications occurred in 4%, comprising fistulas and glans dehiscence without meatal stenosis or strictures.[42]

Uroflowmetry may suggest obstructive voiding (Qmax less than 2 SD, with a plateau curve) after hypospadias repair, regardless of the technique used. A progressive increase in Qmax was documented during 10 years' follow-up in two studies, both of which observed no differences in uroflowmetry between TIP, Mathieu, and MAGPI.[47,48] Together, these add further evidence that the incised plate heals and grows without strictures.

Proximal Hypospadias Repair

We use TIP when the VC is <30° after degloving, although onlay prepucial flap is another option. When there is a

VC of ≥30°, STAG repair is done. Because the degree of curvature may not be apparent at the outset of the operation, initial skin incisions are made to allow any of these options—specifically by preserving most of the foreskin in the event that a graft, or flap, is needed.

TIP

The skin incision dorsally runs parallel to and 4 mm below the corona, and then extends ventrally immediately adjacent to the urethral plate, continuing through the scrotal midline (Figure 73.12a). Because deficient ventral dartos often results in shaft skin adhering closely to the wings of the corpus spongiosum, 1:100,000 epinephrine is injected in the incisions alongside the plate to reduce likelihood for bleeding.

The ventral skin is dissected immediately against its undersurface to further minimize risk for entry into the corpus spongiosum wings on either side of the urethral plate. Skin and dartos dissection continue until the root of the penis is visualized. Scrotal dartos extending up the penile shaft is released.

Then artificial erection is done. A VC of <30° is straightened by a midline dorsal plication using 5-0 polypropylene as described above.

Next, the glans width is measured, and glans wings are developed and dissected laterally to three and nine o'clock as described for distal TIP repair. When the glans is <14 mm wide, more extensive mobilization of the wings is done, continuing the dissection at three and nine o'clock another 4 mm on each side superiorly (Figure 73.12b). The insertion of corpus spongiousum into the wings is also released bilaterally. Our data indicate that complications are decreased by this maneuver for the smaller glans.

The urethral plate is incised deeply to the tunica albuginea of the corpora, extending from the distal tip proximally to within the meatus. As with distal TIP, this incision must be deep to gain the width needed for a normal caliber neourethra (Figure 73.12c).

The urethral plate is then tubularized in two layers. This begins distally with a 7-0 polyglactin stitch placed at approximately the midglans level, which is 3–4 mm below the end of the plate as in distal TIP. As in distal TIP repairs, the opening should be oval, and not rounded. Stitching continues proximally with interrupted subepithelial sutures. Then a second layer of 7-0 polydioxanone is run from proximally to distally (Figure 73.12d). Single-layer urethroplasties, or two-layer tubularizations that run the first layer, have greater risk for fistulas.

When the corpus spongiosum wings are well developed, these are freed sufficiently from the corpora to approximate over the neourethra. Next, the tunica vaginalis is harvested as a coverage flap. We have published that the tunica vaginalis is superior to the dartos in reducing fistulas in proximal hypospadias repair.

A testicle is grasped and then exposed through the scrotal incision using a 15 blade knife to enter its compartment. The tunica vaginalis is opened transversely. A 5-0 absorbable suture placed into the tissues just caudal to the lower pole of the testis provides traction to stabilize it, while 5-0 polypropylene stays lift the corners of the tunica vaginalis cephalad. Dissection proceeds on either side of the spermatic cord, releasing the flap to the external ring, reducing risk for tension on the penis subsequently during erection. Scrotal fat that connects to the flap medially is cut away (Figure 73.12e). Then the testis is sutured back into the dependent scrotum, and its compartment is closed to prevent migration medially toward the penis.

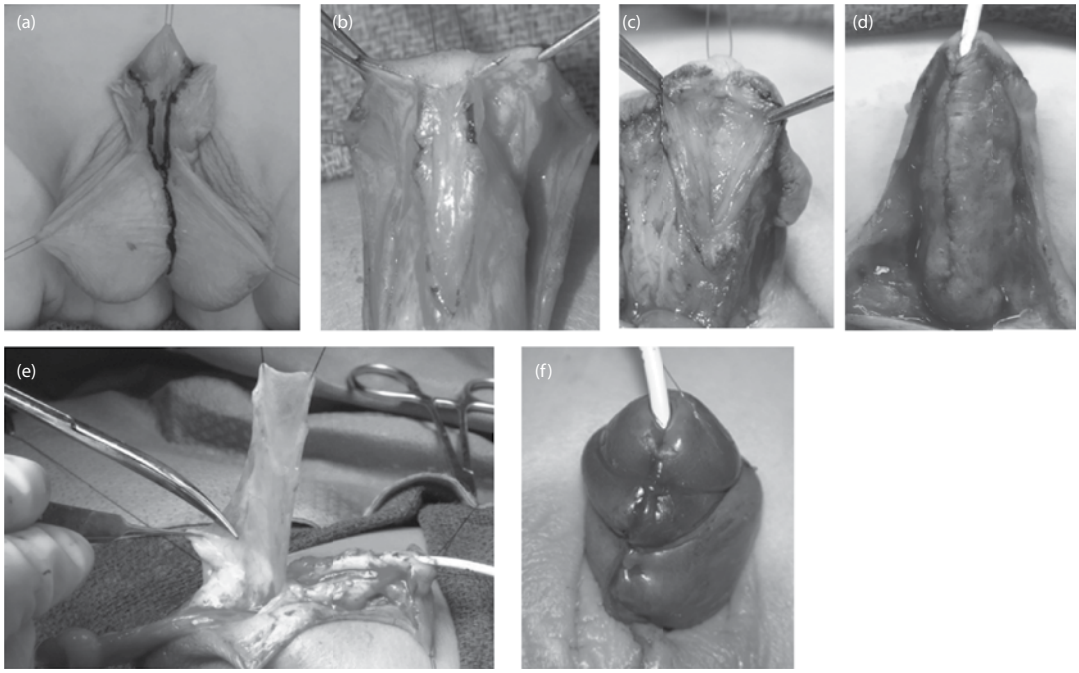


FIGURE 73.12 Proximal TIP repair. (a) Skin incision. Note that it extends alongside the urethral plate ventrally. (b) Extended glans wings dissection. (c) Deep incision of the urethral plate down to the tunica albuginea of the corpora cavernosa. (d) Two-layer subepithelial tubularization of the plate. (e) Preparation of a tunica vaginalis flap to cover the neourethra. (f) Completed repair.

The tunica vaginalis flap is sutured with the inner surface down over the neourethra using 7-0 polydioxanone, since braided sutures entangle the flap.

Glansplasty is done as for distal TIP described earlier, using three interrupted subepithelial 6-0 polyglactin sutures. The first approximates the glans wings distally to create the ventral lip of the neomeatus, and is placed at approximately the midpoint of the glans wings. The next two stitches continue proximally to the corona, with the second stitch including a bite of the tunica vaginalis flap to help keep it in place. The glans wings are not sutured to the underlying neourethra. Glans epithelial sutures are not needed and could create suture marks if used.

It is important in proximal cases to anchor the penoscrotal junction to the corpora on either side of the urethra. Most cases have some penoscrotal transposition, and the visible junction of shaft skin to the scrotum is cut on either side toward approximately three and nine o'clock (Figure 73.13), is pulled downward and medially, and is sutured to the corpora with 5-0 polydioxanone. This simple maneuver helps prevent the penis from "sinking" back into the scrotum and also resolves nearly all cases of scrotal transposition without creating scrotal flaps, which leave visible scars.

Releasing the shaft skin from the scrotum also facilitates cosmetic skin coverage around the penis. The dorsal foreskin is split down the midline to the lower edge of the inner prepucial collar and then sutured there using subepithelial 7-0 polyglactin. Next, the ventral median raphe is created, and finally, excess skin is removed (Figure 73.12f). The catheter provides urinary diversion for 2 weeks.

Results

We published 85% success using proximal TIP in our two most recent series.[49,50] However, our use of this procedure has significantly decreased since we stopped mobilizing the urethral plate for ventral lengthening when the VC was ≥30° to preserve the option to perform TIP urethroplasty. Today, we transect the plate in this common situation and instead do STAG repair due to a higher risk of urethral strictures with TIP when the urethral plate is elevated.

Uroflowmetry has shown progressive improvement in Qmax over time, especially during puberty. One study reported that there was no difference in Qmax 12 years after surgery between TIP, onlay, and tubularized prepucial flaps.[51]

Onlay Prepucial Flaps

The initial skin incision, ventral dartos dissection, and artificial erection with correction of a VC of <30° using plication, and glans wings dissection are the same as described above for proximal TIP.

In the example shown, a double-faced flap is created for urethroplasty and shaft skin coverage (Figure 73.14). 6-0 polypropylene stays are placed at the junction of the inner to outer prepuce, and then the vascular pedicle is dissected from the dorsal shaft skin proximally to the penopubic junction (Figure 73.14a).

Alternatively, the plane between dartos and shaft skin can be developed proximally near the penopubic junction and then dissected distally.

The prepucial flap then is either brought ventrally around the side of the penis in this case (Figure 73.14b), or passed over the glans using a buttonhole in the dartos pedicle.

Then the length of the flap needed to attach to the urethral plate is measured and the inner prepuce trimmed to that size. The proximal end of the flap is sewn to the spatulated native urethra using interrupted subepithelial 7-0 polyglactin. A 6 Fr stent is passed into the bladder and tied to the glans traction suture. Then the flap is gently stretched distally, trimmed as required to maintain uniform dimensions, and sutured to the urethral plate on either side, in the example shown, using a continuous 7-0 polyglactin (Figure 73.14c). The vascular dartos pedicle is used to cover the suture lines.

The flap edges are sutured to the glans wings by subepithelial 7-0 polyglactin. Glansplasty further approximates the glans wings to the corona using interrupted subepithelial 6-0 polyglactin (Figure 73.14d). Scrotoplasty and skin closure can be done as described above for proximal TIP.

In this example, the outer prepuce was maintained on the same vascular pedicle as the inner prepucial onlay flap ("double-faced" flap). This outer prepucial skin flap is sewn to cover the ventral penile shaft (Figure 73.14e).

Urinary diversion is maintained for 10–14 days.

Results

Urethroplasty complications developed in 27%–45% of patients in two series reporting proximal onlay flap repair.[52,53] A systematic literature review identified six studies with 309 patients undergoing onlay flap, which

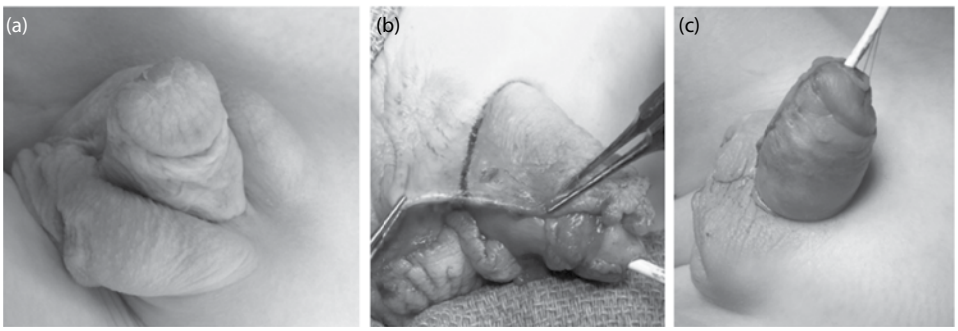


FIGURE 73.13 Correction of penoscrotal transposition without scrotal flaps. (a) Scrotum extending above the penis. (b) Lines for incision from six to ten o'clock and six to two o'clock through the penoscotal junction. (c) Scrotum is rotated down, correcting the transposition without need for scrotal flaps.

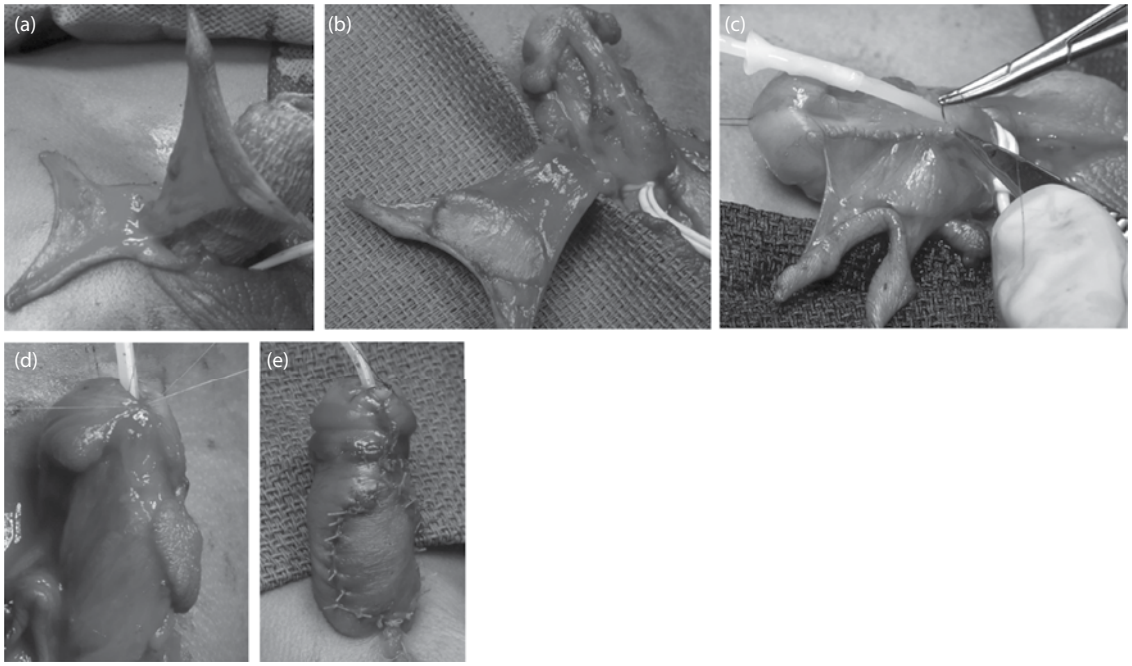


FIGURE 73.14 Onlay prepucial flap. (a) After degloving and correction of a <30° curvature, the prepuce is mobilized from the shaft skin still attached to the underlying dorsal dartos. (b) The flap, in this case with both the outer and inner prepuce, is brought ventrally. (c) The inner prepuce is sewn to the urethral plate to create the neourethra. (d) Glansplasty is done, sewing the glans wings to the end of the neourethra. (e) The outer prepuce is used in this case to provide ventral shaft skin. (Photographs courtesy of Antione Khoury.)

were compared with 262 repaired by TIP, finding no significant differences in their reported complications.[54]

First Stage

Degloving is done as described above for proximal TIP, beginning 4 mm below the corona to preserve most of the prepuce (Figure 73.15a and b). Dissection within the scrotum releases tissue attachments to the formed urethra, which in proximal hypospadias frequently lies superficially and tethered toward the anus. This moves the urethra to a normal location and gains length to reduce the distance to be grafted.

A VC of ≥30° results in transection of the urethral plate at the corona, with proximal dissection off the corpora, continuing past the junction to the formed urethra all the way to the external sphincter (Figure 73.15c and d). This step is also important to eventually gain length for the urethra.

Artificial erection is repeated. A persistent curvature of <30° is corrected by dorsal plication. A persistent VC of ≥30° is straightened by three transverse ventral corporotomies, as described above (Figure 73.15e). The corporotomies are not grafted.

A longitudinal midline incision is made and the glans wings opened widely. It is important that the wings be opened until flat, as this ensures an adequate width of graft to create a neourethra with normal caliber at the second stage. The remaining urethral plate (UP) is excised.

The urethra is gently stretched back distally and sutured back to the corpora using interrupted 6-0 polydioxanone, gaining approximately 1 cm in length. Some or all the UP is preserved, and the opening is spatulated. The distal end of this proximal urethrostomy is sewn to the corpora at twelve, two, and ten o'clock using 7-0 polyglactin.

Skin at the penoscrotal junction is incised from six to approximately three and nine o'clock to release the penile shaft skin (Figure 73.15f). The scrotum is rotated ventrally, reducing transposition, and then penoscrotal or scrotal skin adjacent to the proximal urethrostomy is sutured to the opening at five, six, and seven o'clock with 7-0 polyglactin. The scrotal incision is closed in layers.

Stay sutures hold the corners of the prepuce. The inner prepuce is elevated, and all dartos underlying the graft is excised (Figure 73.15g). Then the proximal shaft skin is brought ventrally around the penis and temporarily approximated at the penoscrotal junction to anchor it while sizing the graft. Next, distal skin is similarly wrapped around the glans, and the graft outline is marked—removing all skin distal to the mucosal collar (Figure 73.15h). These important steps ensure that there is sufficient skin for both the urethroplasty graft and shaft skin closure.

Penile shaft skin is sutured distally to the mucosal collar and proximally at the penoscrotal junction with subepithelial 7-0 polyglactin.

6-0 polypropylene stays are placed in the coronal edges of the glans wings. The widest distal portion of graft is first sewn to glans adjacent to these stays, using subepithelial sutures along the future meatus to avoid suture marks. The graft is next secured to shaft skin on either side using interrupted 7-0 polyglactin (Figure 73.15i). The proximal end of the graft is incised to extend to either side of the urethrostomy.

The graft is quilted to underlying corpora using interrupted 6-0 polyglactin sutures approximately 5 mm apart. The first row extends from the urethrostomy up the midline, with an additional row on either side (Figure 73.15j). Grafts are wider than the corporal bodies, and no attempt

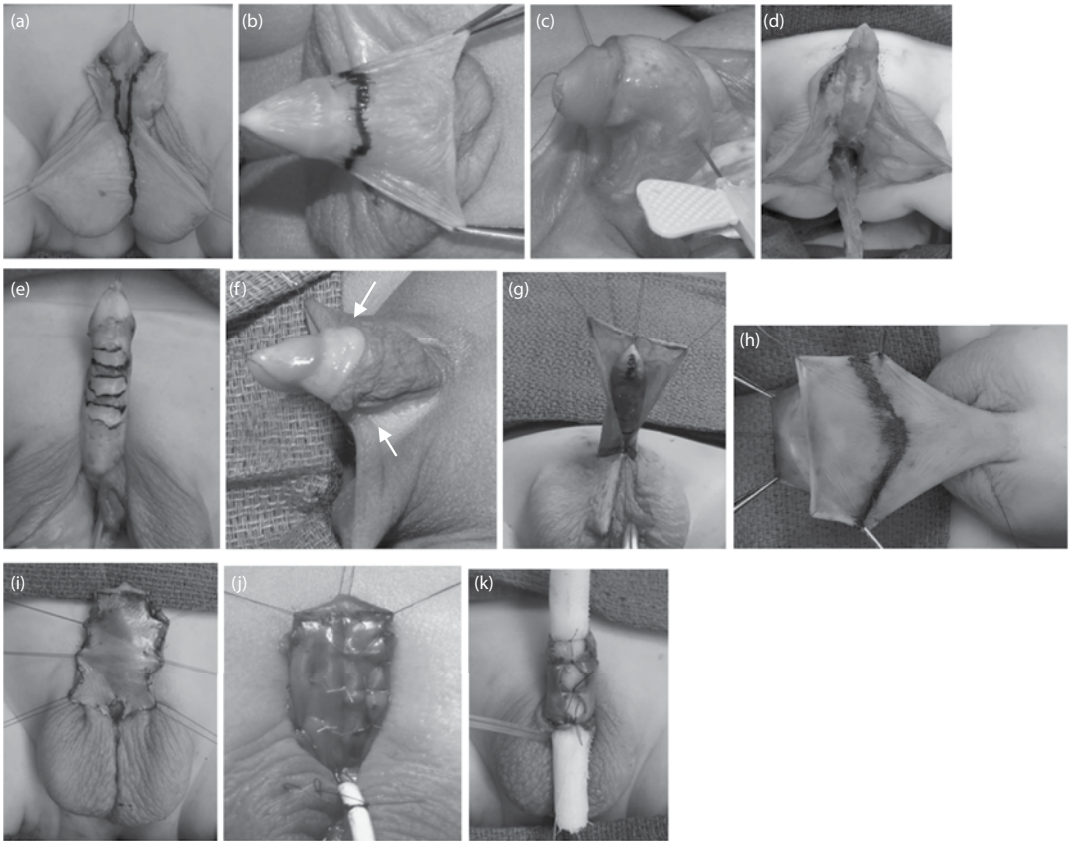


FIGURE 73.15 First-stage STAG repair. (a and b) Initial skin incisions preserving most of the prepuce. (c) Artificial erection after degloving shows a curvature of nearly 90°. (d) The urethral plate has been transected at the corona, and then dissected along with the formed urethra off the corpora to near the external sphincter. (e) Persistent curvature after plate dissection is straightened by transverse corporotomies. (f) Arrows point to the lateral penoscrotal junction, which is released on each side. (g) Dartos has been dissected from the foreskin, which enlarges it. Ventrally, the shaft skin at the penoscrotal junction is approximated temporarily to anchor it into place before harvesting the foreskin graft. (h) The line for removing the foreskin graft has been marked along the coronal margin. (i) The graft has been sewn into the gap from the proximal urethrostomy to the glans tip. Note that the glans is opened flat, like a book. (j) The graft has been quilted to secure it to the underlying corpora. (k) Tie-over bandage provides gentle compression to the graft.

is made to suture them to underlying structures lateral to the corpora to allow easier dissection at the second stage.

An 8 Fr Foley catheter is inserted. Then a rolled petroleum gauze is secured snugly over the graft with a tie-over bandage (Figure 73.15k). The catheter and bandage are removed 7 days postoperatively.

We now instruct caregivers to apply Aquaphor to the entire ventral penis with each diaper change for 3 weeks after bandage removal. Then, 1 month postoperatively, Aquaphor applications are stopped and 0.1% betamethasone ointment is applied ventrally to the graft and adjacent skin twice daily for 3 months. These maneuvers reduce graft contraction.

Second Stage

The second stage is done at 6 months or later. There is no documented advantage to waiting longer than 6 months.

Glans wings are injected with 1:100,000 epinephrine, and then mirror-image incisions are made, extending on each side down the edge of the neoplate and entering the proximal urethrostomy from five to seven o'clock to exclude shaft or scrotal skin sewn there at the first stage. The incision continues down the scrotal raphe (Figure 73.16a).

Glans wings are dissected laterally to three and nine o'clock, and then superiorly another 4 mm off the corpora on each side (Figure 73.16b).

A 6 Fr stent is inserted. Two-layer subepithelial neoplate tubularization is done, using interrupted 7-0 polyglactin and then continuous 7-0 polydiaxanone, as described for proximal TIP. As with TIP, the first suture was placed distally at approximately the midglans level, 3–4 mm below the future meatus, creating an oval, not rounded, opening (Figure 73.16c). Single-layer urethroplasties, or two-layer tubularizations that run the first layer, have greater risk for fistulas.

A tunica vaginalis flap is harvested and dissected proximally to the external ring. The testicle is pexed and its hemiscrotal compartment sutured closed. The flap covers the entire neourethra (Figure 73.16d).

Glans wings are approximated over the neourethra using three interrupted subepithelial 6-0 polyglactin stitches. The first is placed at approximately the midportion of the glans wings, and the last at the corona. As in TIP repair, glans wings are not sutured to the neourethra (Figure 73.16e).

The scrotal wall at three and nine o'clock is sutured to the corpora on either side of the neourethra to reduce transposition and prevent secondary concealed penis.

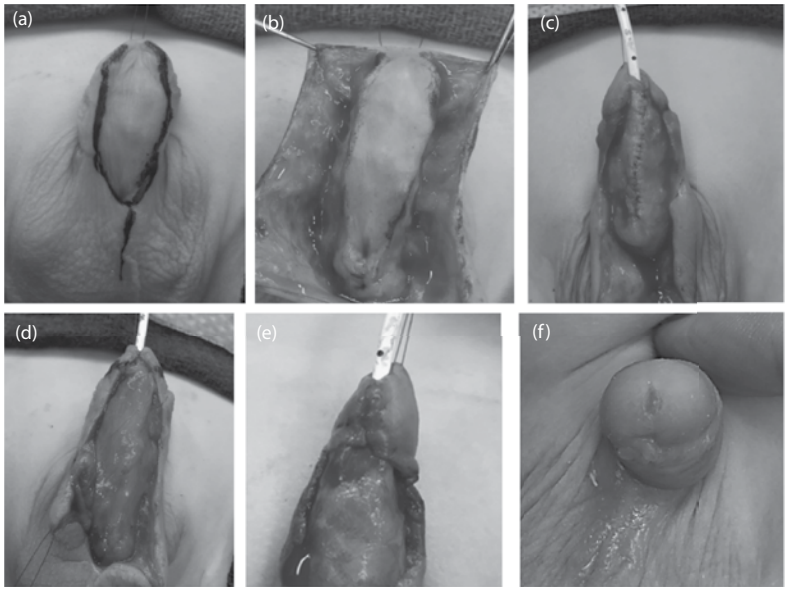


FIGURE 73.16 Second-stage STAG. (a) Line of incision along the graft and down the midline of the scrotum. (b) Extended glans wings dissection for later tension-free closure. (c) Two-layer subepithelial urethroplasty. The first layer is sewn with interrupted sutures, and the second using a continuous suture. (d) Tunica vaginalis, not dartos, covers the neourethra. (e) Completed glansplasty is done as described above for TIP. The neomeatus should be in the normal location. (f) Result 1 year after surgery.

Penile shaft skin is closed in the midline median raphe using interrupted subepithelial sutures. Catheter drainage continues for 2 weeks.

Results

We reported outcomes in 43 consecutive patients with proximal hypospadias,[50] of which 48% had a glans width <14 mm and the VC averaged 70° (30–120). All first stages were successful. Complications following the second stage developed in 24%, primarily glans dehiscence or fistulas that were subsequently corrected for overall 98% success (straight penis, opening at the tip). Glans fusion averaged 3.8 mm (2.5–6).

Others have similarly reported complications in 23%–33% using two-stage graft repairs for patients with a VC of >30°.[55–57]

One-Stage Tubularized Prepucial Flaps and Two-Stage Byars Flaps

Recent publications report complications in the majority of patients after proximal hypospadias repair using foreskin flaps. These ranged from 50% to nearly 85%.[4–6] Given this high rate of complications, the authors suggest that these procedures no longer be used.

Prepucial versus Oral Mucosa Urethroplasty Grafts

Some have expressed concern that there is not sufficient shaft skin and prepuce in boys with proximal hypospadias and a VC of ≥30° to both create a neourethra and cover the penile shaft. This observation may relate, in part, to experience estimating prepucial size before excising the underlying dartos, which definitely increases the epithelial surface area. We have found through experience that there is almost always adequate shaft skin and foreskin for both needs in even the most severe cases (Figure 73.17).

Because of this misperception, oral mucosa has been advocated for primary repair urethroplasty. There are several disadvantages to this approach. First, oral mucosa always heals more thickly than does prepuce, which makes it more difficult to enclose within the glans for a meatus in the correct location, particularly in patients with small glans width. In addition, while there are essentially no donor site complications from circumcision to obtain prepuce, some oral graft harvests will distort the lip and require scar release. If there is partial glans dehiscence after the second stage, the exposed distal urethra is much less noticeable when made of prepuce than oral mucosa, which results in a red meatus that then keratinizes and potentially distorts the urine stream. Finally, should complications develop that require a reoperative substitution urethroplasty, both the foreskin and lower lip will have already been harvested, leaving less optimal options.

We have vast experience using grafts in both primary and reoperative hypospadias repair, and strongly recommend that foreskin be used in primary operations, reserving oral mucosa for reoperations.

Grafts versus Flaps

Throughout the history of hypospadias repair, urologists have generally preferred flaps over grafts for urethroplasty. This is based on the assumption that transferring foreskin ventrally while still attached to the penis more likely ensures its vascularity than removing it and then sewing it back to the penis. These flaps preserve the dartos beneath the epithelium as the "pedicle," even though the dartos does not supply the skin like a mesentery. Duckett's innovation of mobilizing the dartos of his flaps off the

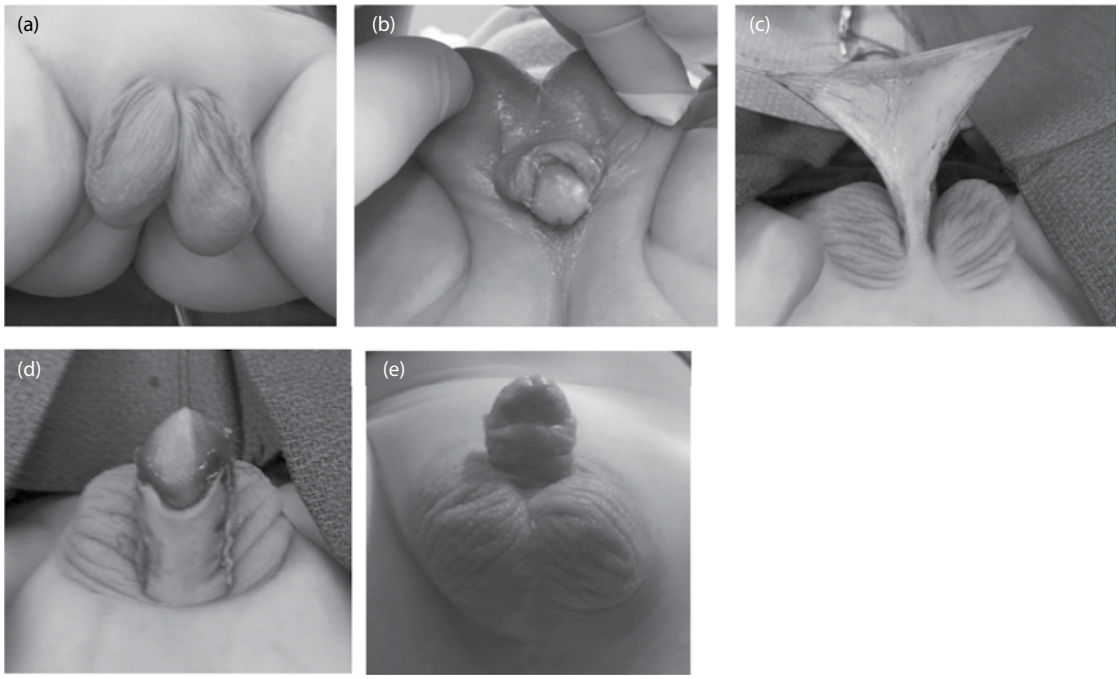


FIGURE 73.17 Perineal hypospadias resembling aphallia. (a and b) Aphallia-like appearance of the external genitalia. (c) Marked deficiency of shaft skin, which was absent ventrally. Note the large foreskin after dartos has been removed. (d) The foreskin graft was sufficiently large to provide tissue for both the neourethra and ventral shaft skin closure. The first-stage suture line of the graft runs along the lateral penis at three and nine o'clock. (e) 18 months after surgery.

dorsal shaft skin proved that dartos does not vascularize penile skin. On the other hand, Duckett commented that fluorescein illumination sometimes showed the ends of his flaps—with their dartos attachments—to be poorly vascularized.[58] Ischemia at the ends of a flap can result in meatal stenosis and/or a proximal anastomotic stricture.

Grafts remained on the fringes of hypospadias surgery, preserved by plastic surgeons who considered their revascularization both reliable and ultimately better than the vascularity of foreskin flaps, which lack a predictable blood supply. All published series of foreskin grafts report graft take after the first stage in 90%–100%. In addition, these series report almost no urethral stenosis, in contrast to meatal stenosis or strictures in 10%–15% of Byars flaps.

W.S. originally used Byars flaps for proximal repairs when VC required the urethral plate to be transected. Fifty percent of these developed a diverticulum, even though none had distal obstruction. In contrast, diverticula have rarely developed after STAG repair, even though both procedures use foreskin. Grafts adhere better to the corpora, like a normal urethra, than do flaps, whose dartos impedes this fixation and therefore promotes turbulent flow and distention of the neourethra (Figure 73.18).

Glansplasty in STAG is the same as in TIP, resulting in a normal ventral length from the meatus to the corona. This measurement has not been reported after flap repairs, but is likely less since the glans wings are stitched to the flap end, which is kept large to reduce meatal stenosis (Figure 73.19).

Finally, removing the dartos from the foreskin allows it to expand, making the graft long enough to reach from within the scrotum to the tip of the glans.

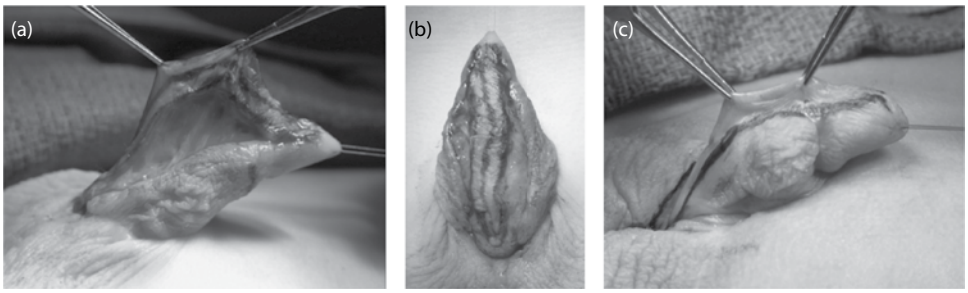


FIGURE 73.18 Byars flap vs. STAG graft. (a) Dartos underlying the Byars flap prevents adherence of the flap to the corpora. Quilting the flap to the corpora has not been reported to be effective. (b) Irregular shape of the flap before tubularization. (c) A graft adheres to the corpora, mimicking a normal urethra. The lateral edges of the graft easily roll together in the midline, creating a smooth neourethra.

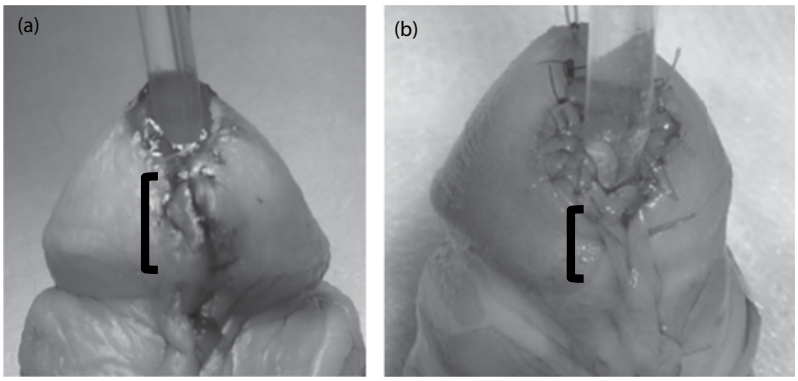


FIGURE 73.19 Glans fusion lengths after STAG vs. an onlay flap. (a) STAG repair creates a normal glans fusion distance from the meatal lip to the corona. (b) Flap repairs suture the glans wings to the end of the urethra, and may result in less, even subnormal, glans fusion.

POSTOPERATIVE MANAGEMENT

Urinary Diversion

There are no differences in urethroplasty outcomes following distal hypospadias repair done with versus without urinary diversion. However, toilet-trained boys are more likely to experience dysuria, urinary retention, and extravasation when diversion is not done.[59] We did distal TIP repairs without a catheter for a period of time, but encountered more secondary phimosis or other unsightly skin swellings, which appeared due to a less secure bandage leaving the distal penis exposed.

There are no trials published regarding need or duration of stenting in proximal hypospadias.

We only use urethral catheters. No study demonstrates a benefit of suprapubic tubes after hypospadias repair.

Bandages

Two studies reported no difference in urethroplasty complications related to bandages.[60,61] We use a "sandwich" bandage, wrapping a small Tegaderm around the penis, which is then gently compressed with a gauze held in place with a larger Tegaderm (Figure 73.20). This bandage falls off spontaneously. We discourage bandages that must be removed by the physician, especially under sedation.

Penile and scrotal hematomas are more likely in teens and adults following hypospadias surgery. We encountered them in nearly 50% of patients initially, which significantly decreased by loosely wrapping the penis with coban.

Hospitalization

Outpatient hypospadias repair became the standard of care in the United States in the mid-1980s. All primary and reoperative surgery can be done without postoperative hospitalization in prepubertal boys. Because of their increased risk for scrotal hematomas, teens and adults remain hospitalized overnight on bed rest.

The authors realize that decisions regarding outpatient versus inpatient repair are potentially influenced by cultural and healthcare system factors. Nevertheless, it is clear that hospitalization is not medically necessary, given that published results in the United States are among the best in the world. It is also clear that many or most caregivers would prefer to return home, if assured by their surgeons that hospitalization is not needed. Regardless, if hospitalization must be done, every effort should be made to minimize bother, fear, and discomfort for the child.

FIGURE 73.20 Typical postoperative bandage.

Preventing Erections

No medical regimen has been reported effective to prevent postoperative erections. We recommend oral diazepam at bedtime to reduce awareness and discomfort of nocturnal erections in older teens and adults.

It is commonly believed that erections in adults may increase the risk for urethroplasty complications. However, we reported outcomes in children and adults to be similar,[62] and boys also have erections following surgery.

Medications

We recommend alternating scheduled acetaminophen with ibuprofen every 3 hours for the first 36–48 hours after repair in infants. After age 1 year, we use hydrocodone

(which includes acetaminophen) rather than acetaminophen alone.

Boys over 1 year are also prescribed oxybutynin two or three times daily during urinary diversion, to reduce painful bladder contractions.

There are limited data regarding postoperative antibiotics to prevent urinary tract infection (UTI) or wound infection. We recommend sulfamethoxazole/trimethoprim during urinary diversion.

COMPLICATIONS

Many urethroplasty complications occur because of surgeon error, which emphasizes the responsibility to do the key steps of procedures according to descriptions with the best published outcomes. In contrast, complications are rarely due to the patient or caregivers.

In general, correction is delayed for 6 months after prior surgery, to allow tissue healing before additional surgery.

Fistulas

Prevention

Subepithelial, two-layer urethroplasty and coverage by a barrier flap have been shown to reduce likelihood for fistulas. We published a significant reduction in fistulas in proximal repairs using two-layer tubularization: the first layer interrupted and the second continuous. Similarly, the tunica vaginalis was more effective than the dartos in preventing fistulas in proximal repairs. With these maneuvers, fistulas should occur in <5% of cases.[49] Surgeons using other methods, such as single-layer urethroplasty, two-layer urethroplasty with a running closure reinforced with interrupted sutures, and/or dartos flaps, should review their results to be certain their fistula rate is not greater than 5%.

We have also found that recurrent fistulas after proximal repairs often indicate a persistent VC of ≥30°. These fistulas were noted within or just distal to the curvature, suggesting that tension during erections caused focal wound separation.[35]

Treatment

The first step in fistula closure is assessment for additional complications, including distal stenosis, diverticulum, and/or VC. Most fistulas, especially following distal repairs, are isolated; that is, there is no distal obstruction. Correction involves closure of the urethral defect and coverage with a flap. Traditionally, fistula repair has been done via a small incision around the defect with advancement of a skin flap over the closed urethral defect. We make a larger midline incision, which improves exposure, facilitates creation of a ventral dartos flap for coverage, and enables excision of redundant skin that often develops around the fistula with median raphe closure (Figure 73.21).

We also reported that subcoronal fistulas below an intact glans can be closed without redo glansplasty or urinary diversion with 95% success.[63] If the glans wings are dehisced with only a bridge of skin between them, fistula closure requires reoperative urethroplasty and glansplasty (Figure 73.21d).

Glans Dehiscence

This common complication is underreported. It is defined as complete separation of the glans wings with or without a bridge of skin between them (Figure 73.22). Glans dehiscence re-creates a hypospadias defect, with suboptimal aesthetic appearance and increased risk for a deflected or spraying stream.

Prevention

Mattress sutures do not prevent glans dehiscence, but do increase risk for suture marks or glans injury, and so should not be used. Glans wings dissection, as described in this chapter, opening laterally to three and nine o'clock and then superiorly an additional 4 mm bilaterally, effectively elongates the wings and reduces tension on their approximation over the neourethra.[18,50]

Treatment

Repair requires hypospadias reoperation as described below, most often by reoperative TIP. Secondary repair is

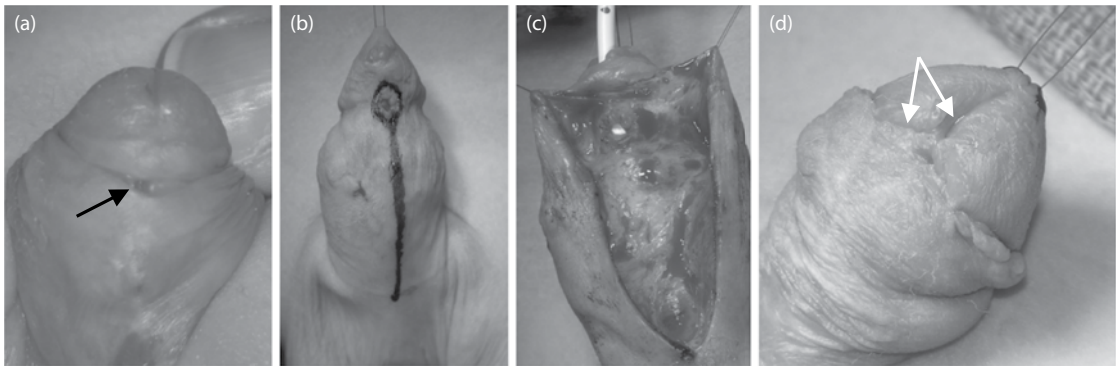


FIGURE 73.21 Subcoronal fistulas. (a) Subcoronal fistula with normal glans fusion. There is no need to reopen the glans to close the fistula. (b) Incision around the fistula and down the median raphe, giving exposure to close the fistula, create a dartos coverage flap, and revise any redundant ventral shaft skin. (c) Excellent visualization of the fistula, which can now be closed and covered with a dartos flap extending beyond it distally. (d) Subcoronal fistula with partial glans dehiscence. In this case, redo TIP repair is needed to both close the fistula and correct the dehiscence.

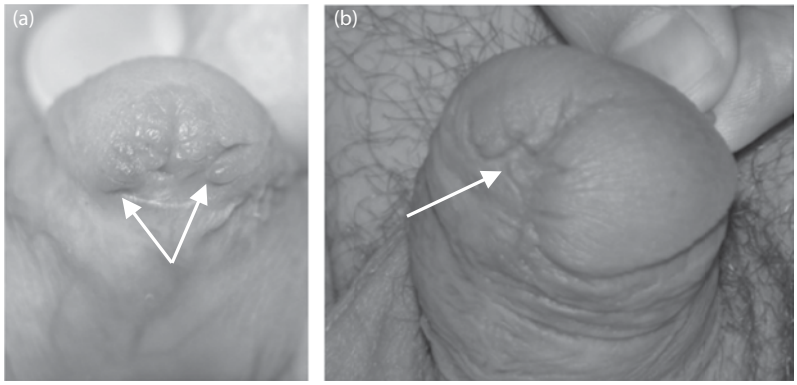


FIGURE 73.22 Glans dehiscence. (a) Complete separation of the glans wings indicated by the arrows. (b) Complete separation of the glans wings, with an intervening skin bridge (arrow) giving the false appearance of a glanular meatus.

successful in more than 75%. If glans dehiscence recurs, we do not do a third glansplasty, as success is less than 50% and there is risk for glans loss.

Meatal Stenosis

This complication is likely overdiagnosed. A small-appearing meatus with a fine stream most often does not indicate anatomic obstruction, especially early after surgery when there is edema of the neourethra (Figure 73.23). As discussed above, uroflowmetry after hypospadias repair may show an "obstructive" pattern initially, which improves progressively—indicating that there was no stenosis.

We define meatal stenosis as a caliber of <8 Fr with symptoms (persistent stranguria, urinary retention, and UTI).

Prevention

We reported no meatal stenosis after either primary TIP or STAG repair, and other similar series also found stenosis in 3% or less of cases. This suggests that meatal stenosis should first be considered a technical error: inadequate urethral plate incision and/or tubularization too far distally.

Treatment

There are no published data indicating that meatotomy is effective for true meatal stenosis after hypospadias repair. If meatotomy is done, the incision should be made dorsally, as a ventral incision may re-create the hypospadias.

Otherwise, relief of meatal obstruction requires hypospadias reoperation, generally a STAG repair with oral graft, as described below.

Neourethral Stricture

Strictures of the neourethra are defined as near-complete closure of the lumen. They are rare after TIP or STAG repairs, but were reported in 12% and 14% of two reports on Byars flaps.[4,5] Strictures are usually diagnosed due to stanguria, urinary retention, and/or UTI. We do not subject boys with these symptoms to urethrography, but rather rely on urethroscopy under anesthesia to establish the diagnosis.

Prevention

As stated, strictures are rare after TIP and STAG, and may be an inherent risk with prepucial flaps.

Treatment

Therapeutic dilation should not be used in boys. The treatment is not curative, and causes great anxiety and discomfort.

A single direct-vision urethrotomy is reported to have 25% effectiveness for hypospadias strictures of <1 cm long. Repeat urethrotomy for failures was not successful.[64]

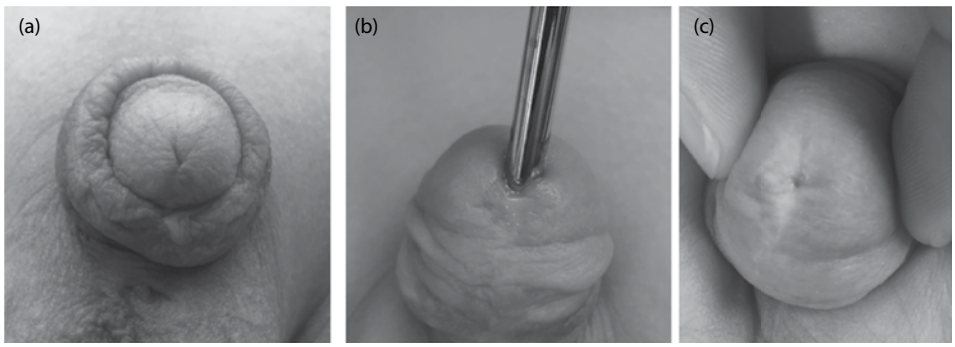


FIGURE 73.23 Meatal stenosis. (a and b) Small-appearing meatus is not meatal stenosis, as shown by easy passage of a 12 Fr sound. (c) True meatal stenosis is smaller than 8 Fr.

Therefore, strictures after hypospadias repair are best managed by open surgery, using an inlay graft if the stricture is not obliterative, and excision of the lesion with reoperative STAG when it is. These are discussed below.

Diverticulum

A diverticulum is visible ballooning of the neourethra during voiding (Figure 73.24). This complication is also rare after TIP and STAG, but more common following prepucial flap repairs. Despite widespread opinion, these indicate distal obstruction; most occur without distal obstruction.[65]

Prevention

We know of no technical maneuver to reduce the likelihood that a diverticulum will develop after a flap repair. This was the main reason W.S. stopped using Byars flaps.

Treatment

Although distal obstruction is uncommon, the first step in the procedure is to calibrate the urethra distal to the diverticulum. Then a ventral midline incision is made over the diverticulum, preserving the dartos for a coverage layer. The diverticulum is opened longitudinally, the excess tissue is excised, and then the urethra is closed in two subepithelial layers as described for proximal urethroplasties. The dartos is sutured as a barrier layer over the closure. We use urinary diversion for 1 week. Recurrences after repair are uncommon.[65]

FIGURE 73.24 Diverticulum.

Recurrent Ventral Curvature

A recurrent VC of ≥30° almost always indicates inadequate initial correction. Dorsal plications are not reliable for durable straightening of a VC of ≥30° (Figure 73.25). Excision of the urethral plate does not guarantee that the penis is straight. Ventral lengthening by three transverse corporotomies is the most reliable means for durable straightening.

Prevention

As discussed above, a VC of ≥30° after degloving should next lead to urethral plate transection at the corona, and its dissection from the corpora. A persistent VC of ≥30° after transection of the urethral plate should be straightened by three transverse corporotomies.

Treatment

A recurrent curvature of ≥30° requires the neourethra previously created to be excised, along with all other ventral scar tissue that is encountered. Repeat artificial erection may demonstrate straightening, or a VC of <30°, determined using a goniometer, that can be straightened by dorsal plication. However, a VC of ≥30° after excising the neourethra requires ventral lengthening using three corporotomies. Reoperative STAG repair is done using lower-lip mucosa for the urethral graft, which is described in the next section.

The fact that correction requires removal of the neourethra with two-stage reoperative grafting using oral mucosa emphasizes the critical importance of optimally straightening VC at the initial operation.

FIGURE 73.25 Recurrent VC. Curvature recurred despite dorsal plication. The plication suture is visible (arrow) and in the correct location.

HYPOSPADIAS URETHROPLASTY REOPERATIONS

Preoperative Assessment

Important factors to determine after failed hypospadias repair include the original meatal location, the means used to straighten the associated VC, the number of prior operations and date of the most recent one, and the techniques used. Generally, reoperations are delayed until 6 months after the last procedure. Even a single reoperation doubles the risk for additional complications, and if a patient has had three or more repairs, the complication rate increases to 40%.[7] The relative rarity of reoperations and the high risk for more complications indicates that these, like proximal hypospadias repairs, should be specialized to high-volume hypospadias surgeons.

Physical exam determines if the penis feels tethered, or is overtly curved, and the meatal location. All apparent complications, such a fistulas and glans dehiscence, are noted. The visible extent of scarring is recorded, as is deficiency of the shaft skin, especially ventrally.

We do not perform urethrography, or cystoscopy as a separate procedure, as sufficient evaluation to determine all complications can be made intraoperatively at the time of reoperation.

We also do not recommend androgen stimulation, given a lack of evidence that it reduces complications and the possibility that testosterone may increase the risk for poor outcomes.

Surgical Algorithm

Hypospadias reoperations should be approached systematically (8). As with primary repairs, VC drives decision making. When there is <30° after degloving and release of contracted scar, TIP is the first consideration. If there is a VC of ≥30°, the neourethra and all ventral scars must be removed, the penis straightened, and then STAG performed (Figure 73.26).

The most common indication for hypospadias reoperation is glans dehiscence. If the urethral plate appears supple, without gross scars, then a reoperative TIP repair is done. If prior surgery removed the urethral plate, then the skin neoplate is TIP incised dorsally, and the resulting defect grafted using the upper lip for one-stage repair. This inlay graft is a modification of TIP, essentially a G-TIP done using oral mucosa. Because the graft is sewn dorsally to the corpora and the lateral edges of the neourethra remain vascularized, one-stage tubularization can be done. Oral inlay grafts should be harvested from the upper, not the lower, lip—preserving the lower lip should there later be a need for a two-stage replacement urethroplasty.

Inlay grafts are also the first treatment for nonobliterative neourethra strictures. However, they are less effective for meatal stenosis, since it is difficult to place sufficient oral graft to open the narrowing at the meatus without placing graft distally onto the glans past the meatus. In these cases, STAG repair is needed to excise the scar and place a wide sheet of oral mucosa within the glans out to the meatus.

In addition to a VC of ≥30° and meatal stenosis, other indications for STAG reoperation include gross scarring of the neourethra, obliterative strictures, hair in the neourethra, and balanitis xerotica obliterans (BXO).

Some additional principles guide our approach to reoperations. For example, when Mathieu or onlay flaps have been used, we excise them and perform TIP. When there are indications for substitution urethroplasty, we completely remove the neourethra, even if a segment appears healthy, to create a continuous neourethra with uniform composition rather than a composite of various tissues. Otherwise, complications such as diverticulum potentially can result from the varying elasticity of the tissues incorporated together, or strictures may develop at the junctions of those tissues. We do not use skin flaps in reoperations, in part because there often is insufficient skin after prior surgery for both urethroplasty and shaft skin closure, and also because vascularity of previously operated tissues is not reliable.[66]

TIP

A Y-shaped incision is outlined extending along the visual borders of the glans wings to the urethral plate, joining approximately 2 mm below the meatus, and continuing down the median raphe toward the proximal shaft (Figure 73.27). It is usually not necessary to circumferentially deglove the penis in reoperations, which we do only when there is excess dorsal skin to revise or persistent curvature to straighten after the ventral skin incisions are made.

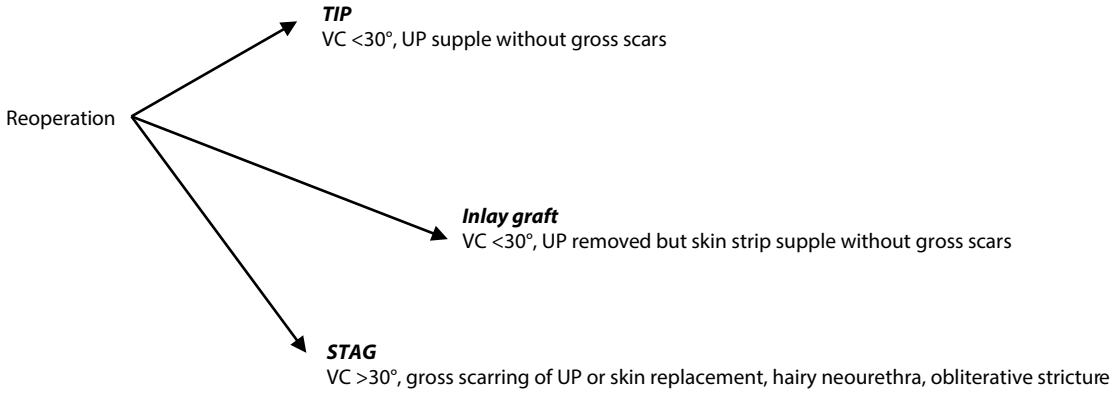


FIGURE 73.26 Algorithm for hypospadias reoperations. UP: urethral plate.

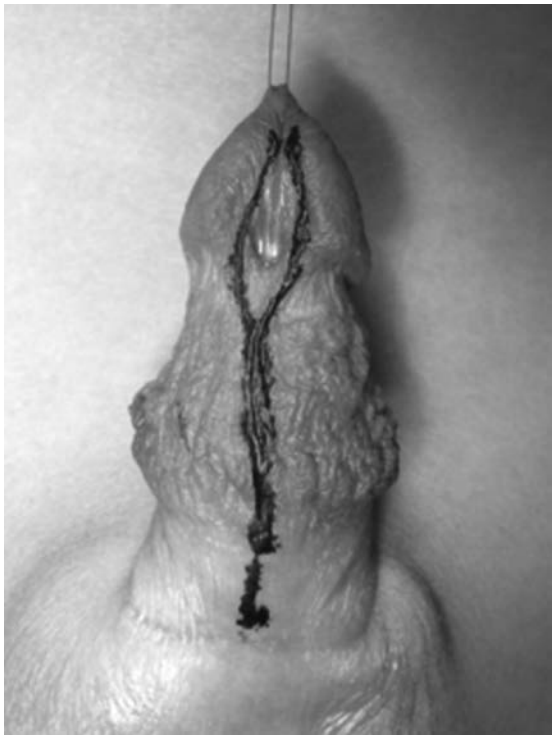


FIGURE 73.27 Incision for reoperative TIP repair.

The glans incision lines are injected with 1:100,000 epinephrine, and then the glans wings are developed. Since most reoperations have glans dehiscence, the extended dissection method is done first to three and nine o'clock, and then superiorly on each side another 4 mm.

Dissection down the median raphe is done immediately under the shaft skin to preserve ventral dartos for later flap coverage over the neourethra.

If a flap was previously used to supplement the urethral plate, as in Mathieu or onlay procedures, it is removed.

The urethral plate is next incised in the midline, deeply as for primary repairs, and a 6 Fr stent is passed into the bladder and tied to the glans traction suture. Tubularization is done in two subepithelial layers, using interrupted stitches for the first layer, followed by a continuous second layer. As in primary TIP, the first stitch is placed at approximately the midglans to avoid iatrogenic meatal stenosis.

A ventral dartos, or tunica vaginalis, barrier flap is created for distal and proximal repairs, respectively, and extended over the entire neourethra.

Glansplasty is done as previously described using three interrupted subepithelial stitches.

Excess ventral shaft skin, when present, is excised and the median raphe sutured closed with subepithelial 7-0 polyglactin interrupted stitches. The stent provides urinary diversion for 10 days.

Results

Reported complication rates range from 12% to 30%.[67–69] We published results in 69 patients with a mean of 1.1 (1–3) failed repairs, of which most originally had distal hypospadias. Complications developed in 19%.[67]

One-Stage Dorsal Inlay Grafts

The initial incisions, ventral shaft dissection, and glans wings development are done as described above for reoperative TIP. A first-generation cephalosporin is administered when oral graft harvest is anticipated.

The skin strip substituting for the urethral plate is incised dorsally in the midline as for TIP repair, extending into the native urethra. 7-0 polypropylene stays are placed laterally at its midpoint, providing traction to expose the dorsal defect. The visible margin of the upper lip is marked, and two 5-0 polypropylene stays are used to retract the lip open and upward. The needed graft is outlined, and then 1:100,000 epinephrine is injected before incision.

The graft is removed by dissection above the muscle, and then defatted. These smaller grafts are most easily handled by wetting an area on the drapes, which then holds the graft still. Tenotomy scissors cut the excess fat from underneath the epithelium. The donor site is not sutured and will reepithelialize.

We intentionally select the upper lip for inlay grafts, as they are thinner than cheek grafts. Although success with inlay grafts is high, the potential that a substitution urethroplasty might be needed in the future prompts us to preserve the lower lip. We strongly discourage harvest of small grafts from the lower lip.

7-0 polyglactin anchors a distal edge of the graft to the proximal end of the defect within the urethra. The graft is then sewn to the perimeter of the dorsal incision with interrupted epithelial 7-0 polyglactin stitches proceeding distally and trimming excess graft as needed. Finally, quilting sutures fix the graft to the corpora, first at 5 mm intervals down the midline and then to either side as needed (Figure 73.28).

FIGURE 73.28 Inlay graft reoperation.

A catheter is passed into the bladder and tied to the glans traction suture. Tubularization is done in two subepithelial layers, the first using interrupted 7-0 polyglactin and the second continuous 7-0 polydioxanone. The first stitch is placed distally at approximately the midglans so that the opening is oval, not rounded, to avoid iatrogenic stenosis.

A barrier flap is created from the ventral dartos, or tunica vaginalis if there is insufficient dartos or a proximal repair, placed over the entire neourethra, and sewn in place.

Glansplasty is done distally, creating the ventral lip of the neomeatus at the midpoint of the glans wings, and continuing proximally to the corona using interrupted subepithelial 6-0 polyglactin. Most often, three stitches are required. As with TIP repairs, the glans wings are not sewn to the neourethra. The second stitch incorporates the barrier flap to hold it in place.

Any excess shaft skin is next excised, and then subepithelial skin closure completed. Urinary diversion continues for 10 days.

Results

Three institutions all report complications in 15% of cases after inlay graft reoperations.[67,70,71] Of these, the mean number of prior operations was two in two series, and four in the other. Two of these noted postoperative strictures at the junction to the formed urethra, which likely emphasizes the need to incise the skin strip well into the urethra until healthy tissues are encountered.

Stag Reoperations

First Stage

A first-generation cephalosporin is administered intravenously when oral graft harvesting is anticipated. The orogastric tube is secured laterally to leave access to the lower lip, or nasogastric intubation is performed depending on anesthesia preference.

As with the other reoperations described above, the initial incision most often is ventral using a Y to create glans wings and open the skin down the median raphe. Complete degloving usually is not needed, although it is done when VC persists after the neourethra and surrounding fibrosed tissues are excised to better assess and correct the bending.

Next, the neourethra is opened from distally to proximally to normal urethra and then completely excised. All underlying scar tissues are removed down to the tunica albuginea of the corporal bodies. The visual margins of the glans wings are injected with 1:100,000 epinephrine before their incision. Glans wings are created and dissected laterally to three and nine o'clock. Extended dissection to additionally free the wings from the corpora distally is not done at the first stage, but the glans should be opened widely like a book in order to place a sufficient amount of graft into the glans. Prior surgery sometimes leaves the ventral glans flat, but excision of the neourethra and associated scar tissue reestablishes a deep groove between the wings so that the ultimate neomeatus will be vertical and slit after the second stage.

An artificial erection must be checked after excision of the neourethra; excision alone does *not* guarantee straightening. A persistent curvature of $\geq 30°$ after degloving and removal of the neourethra and ventral scar tissues is corrected by three transverse ventral corporotomies.

The normal urethra is spatulated ventrally, and proximal urethrostomy made by suturing adjacent skin to the urethra at five, six, and seven o'clock using 6-0 or 7-0 polyglactin in children and 5-0 in adults.

The visible border of the lower lip is marked with a pen, and two 5-0 polypropylene stays are placed into this line to retract the lip open and down, exposing the inner surface. A damp gauze is packed adjacent to the endotracheal tube to block blood from the throat. The graft is outlined running adjacent to the gum proximally, within 2 mm of the visible lip margin distally, and at a visible junction to cheek mucosa on each side laterally (Figure 73.29a). The goal is to remove all lip mucosa within these anatomic boundaries.

This graft will reach from the tip of the glans distally to deep within the scrotum proximally. Epinephrine (1:100,000), or bupivacaine with 1:200,000 epinephrine, is injected under the entire graft prior to harvest for hydrodissection. Then an incision is made first along the gum, then the lip, and finally the lateral edges by the cheek, so that blood running down does not obscure dissection. The correct plane to harvest the graft is above the muscle, limiting fat that is most abundant near the outer margin of the lip. The donor site is not sutured or otherwise treated. The wound heals by reepithelialization, leaving a fine transverse scar (Figure 73.29b).

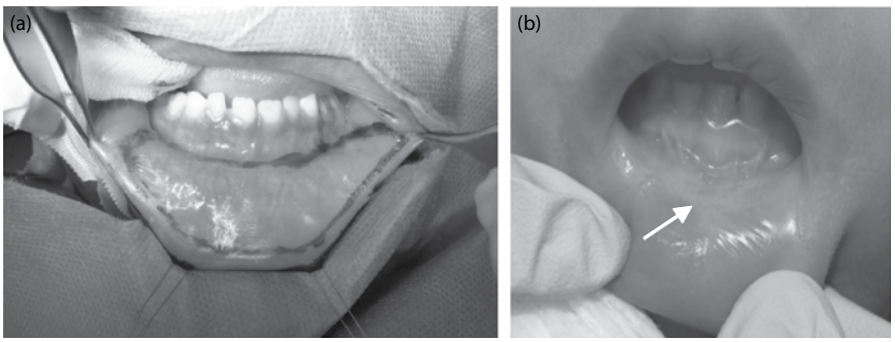


FIGURE 73.29 Lower-lip graft. (a) If a smaller graft is needed, harvest should be from the upper lip. The wound is not sutured, but allowed to heal by secondary intention. (b) Arrow shows the transverse scar after healing.

The graft is next defatted. There is no need to pin it to a board, as it is sufficient to simply drape the graft over the index finger. This allows the surgeon to sense the depth of the dissection and avoid holes.

Finally, the graft is sutured into place beginning distally. First, it is sewn to the coronal margin adjacent to the glans wings stays on either side with 7-0 polyglactin in children or 5-0 in adults, and then gently stretched further distally and stitched to the end of the glans. These most distal stitches are subepithelial on the glans side to avoid suture marks in the future neomeatus. Generally, the graft measures between 13 and 20 mm wide at the level of the corona. Not placing sufficient graft in the glans is a significant technical error.

Next, the graft is stretched gently proximally and sewn with interrupted polyglactin to shaft skin toward the meatus. The proximal end is split up the midline to place graft to either side of the urethrostomy, where it is stitched. Once the perimeter of the graft has been sewn into place, the graft is quilted to the corpora using 6-0 polyglactin in children, or 5-0 in adults, both on a RB1 needle, which we have found best penetrates the graft and secures it to the underlying tunica albuginea. Quilting is first done down the midline, and then to either side between the midline and perimeter, with interrupted stitches approximately 5 mm apart in children and 1 cm in adults.

Occasionally, the relative sizes of the lip graft and penis width are such that the usual graft will not entirely fill the defect in a single sheet of tissue. When more than one piece is needed, they should be joined on the shaft, below the coronal region, obliquely, to reduce chances for scar contracture. Lip graft is placed within the glans, since it is thinner than the cheek, which is used on the lower penile shaft.

5-0 polypropylene stays are placed at the graft perimeter adjacent to the meatus and at the middle section. A catheter is passed into the bladder, and then a rolled Vaseline gauze is laid onto the graft and tied snug, not tight, with the polypropylene stays.

The tie-over bandage and the catheter are removed in 1 week. In younger, active children, the polypropylene stays often pull loose and the bandage usually falls off spontaneously before 1 week. Those bandages that remain in place often develop an offensive odor, which has not indicated infection, graft loss, or other complications.

Teens and adults stay in the hospital for overnight bedrest after oral mucosa harvesting, primarily to reduce risk for scrotal hematomas. There can be significant mouth discomfort after oral harvest, which is diminished using Magic Mouthwash, a mixture of lidocaine, Maalox, and Benadryl.

After the bandage is removed, Aquaphor is applied to the graft and adjacent shaft skin several times daily to keep them moist. Beginning 1 month postoperatively, 0.1% betamethasone ointment is instead applied twice daily for another 12 weeks.

Oral mucosa keratinizes, when dry, create a superficial snakeskin appearance. This is of no consequence before the second stage.

Results

Graft contracture or loss requiring reoperation to repair or replace the graft occurs in <10% of cases.[8] Partial transverse contractures can be corrected during the second stage by either inlay grafting or inclusion of adjacent supple and non-hair-bearing skin into the urethroplasty.

However, longitudinal contraction causing penile bending of ≥30° requires staged graft repair or replacement. This most often occurs around the midshaft, where a transverse incision is made through the graft and then the remaining proximal graft and urethrostomy are mobilized off the corpora. Distal healthy graft on the distal shaft and within the glans can be preserved. Once the scar is all released and excised, the penis should be straight with artificial erection. A patch graft of oral mucosa from the upper lip or cheek is used to fill the gap between healthy distal graft and the now relocated proximal urethrostomy, which is quilted into place and further secured with a tie-over bandage. Second-stage urethroplasty is delayed another 6 months.

The most common donor site complication is contracture of the scar causing visible lip distortion. This usually resolves before the second-stage procedure, but if it persists, two or three longitudinal incisions can be made through the linear scar to release it.

Second Stage

Second-stage tubularization is done 6 months later. The desired neourethral plate appearance is seen in Figure 73.30. The border of the neoplate is outlined with a marking pen, creating a U shape. The glans wings are injected with 1:100,000 epinephrine, and then the incision made. Glans wings are dissected initially to three and nine o'clock. The proximal aspect of the incision just enters the urethrostomy, to exclude the skin previously sutured there, from five to seven o'clock. Then the incision continues below the urethrostomy, dividing the median raphe of the scrotum for later access to a testicle to harvest tunica vaginalis.

FIGURE 73.30 Appearance of oral mucosal graft prior to 2nd stage urethroplasty. Well-healed lower-lip graft. Note it appears relatively more thick than prepucial grafts.

There is little need to dissect under the edges of the neoplate, as they are most often sufficiently mobile for tubularization, and extensive dissection theoretically could devascularize that region.

Dissection of the glans wings laterally to three and nine o'clock, and then cephalad off the corpora bilaterally for approximately 4 mm, is done routinely in these cases for later tension-free approximation.

A catheter is passed into the bladder and tied to the glans traction suture as detailed above for second-stage STAG repair with prepucial grafts. The neoplate is tubularized in two layers, the first using interrupted subepithelial 6-0 polyglactin and the next continuous 6-0 polydioxanone in children, or 5-0 sutures in adults. The initial stitch is placed distally at approximately the midglans level to create an oval, not rounded, opening.

Next, a testicle is exposed and its tunica vaginalis covering dissected to the external ring. The testicle is pexed back into its normal location, and the scrotal dartos is sutured closed over it. The tunica vaginalis flap is placed with the inner portion over the neourethra and tacked into place with interrupted 7-0 polydioxanone stitches.

Glansplasty is completed beginning distally to establish the proximal lip of the neomeatus. Interrupted subepithelial 6-0 polyglactin is used in children or 4-0 in adults, and as in primary TIP repair, the glans wings are not sutured to the neourethra. The first stitch is at approximately the midglans. Closure continues proximally to the corona with two additional sutures, the second including a bite of the tunica vaginalis flap to hold it in place.

Glansplasty should enclose all the oral mucosa, as any exposed regions at the meatus will chronically keratinize, producing a snakeskin that the patient will peel off repeatedly, and which can deflect the stream.

Skin closure down the median raphe is then completed using 7-0 subepithelial polyglactin. A Tegaderm bandage is applied. The catheter provides urinary diversion for 2 weeks.

Results

Complications occur in nearly 40% of patients, most of whom are considered hypospadias cripples after failing an average of four repairs in our series.[8] In another series of STAG reoperations, one-third of patients had BXO,[72] which has a high rate for additional complications even after excision and staged oral grafting.[73] Our complications included glans dehiscence and fistulas, with no urethral strictures or diverticulum.

DURABILITY OF PREPUBERTAL REPAIRS

Most hypospadias repairs are completed during childhood. Of these patients, some will have no future problems, others will have persisting complications into adulthood, and a third group, considered successfully repaired, may present as adults with a "new" complication. Barbagli et al.[74] reported on 60 adult patients with childhood hypospadias repairs seen over a period of 9 years. Of these, some had visible penile deformities, that is, persisting complications, while others who appeared satisfactorily repaired presented with symptoms more than 10 years after surgery and were diagnosed with urethral strictures. The authors theorized that this latter group developed strictures after the onset of sexual activity from "repeated stretch and trauma" to the skin-made urethra lacking corpus spongiousum.

Subsequently, Ching et al.[75] reported their experience with 55 adults with hypospadias accumulated over 16 years, of which 16 were considered late failures. Their findings were not specifically described, but the authors also concluded that childhood repairs may not be durable.

These comments have found their way onto the Internet, and from there into layperson Facebook groups, raising questions of whether hypospadias should be repaired in childhood if the results do not last through growth and the onset of sexual activity during puberty. Consequently, some mothers now ask if surgery should be postponed until puberty.

Despite calls for routine long-term follow-up after repair of infants continuing through puberty, there is to our knowledge no study, even from countries with national healthcare systems, that captures the majority of patients operated on with periodic assessments for this duration of time.

It is also noteworthy that the majority of adult patients with hypospadias reported by adult reconstruction specialists had strictures, which is not surprising given that their centers are known for expertise in stricture repair. The duration of the anatomic lesion before diagnosis with symptoms is difficult to know with strictures, and certainly, it is possible that some of these men developed strictures before puberty. Even if all these strictures developed from sexual trauma, delaying surgery until puberty would not avoid the risk for future strictures unless patients are instructed not to have sexual intercourse indefinitely.

It is useful to place this discussion into context. Barbagli recently combined his experience with that of another center to report the largest series of adults with hypospadias, a total of 1176 men from a 19-year period, averaging 62 per year.[76] The authors did not state how many of these were considered to have late failures after beginning sexual activity. If all of them were, those 62 would represent less than 1% of the approximately 10,000 boys who undergo hypospadias repair each year in the United States alone.

The adults we see with complications after childhood repair each have had persisting complications, rather than new-onset ones.

IMPROVING HYPOSPADIAS REPAIR

Hypospadias repair is a complex operation, requiring precision. Dissection even 1 mm in the wrong plane during the key steps of a technique potentially increases the risk for complications. Current data reviewed in this chapter indicate that approximately 1 of every 10 distal repairs and more than 50% of proximal repairs will develop complications, requiring additional surgery. Furthermore, the risk for additional complications doubles with the first reoperation and rises to 40% by the third.

It is clearly important to achieve success with the primary repair. This section discusses the means for individual surgeons to improve their results.

Limit the Surgical Algorithm

It was previously believed that surgeons had to choose from among a variety of procedures for the one best suited to the specific anatomy of the patient. In fact, selection of the wrong technique, rather than technical error, was described as the leading cause of complications.[77]

In contrast, we discuss above that all repairs can be done by adapting TIP and STAG to the situation encountered, and emphasize that complications most often are the result of technical error. A limited algorithm simplifies decision making, and allows the surgeon to primarily focus on performing the key steps, optimally to reduce technical error. Even those surgeons who prefer other techniques can limit the total number of procedures they use to only a few and concentrate on their optimal performance.

Given that the average number of distal repairs done by U.S. pediatric urologists is only one a month, the advantage of using a single technique with published success in more than 90% of cases is clear—surgeons can gain expertise that is not as easily achieved and maintained if multiple techniques are each used a few times a year.

Perform the Key Steps Optimally

Every surgeon performing a hypospadias repair technique should do each key step according to the best published results. Failure to do so results in increased risk for complications, and reviews of operative records in patients presenting to us after failed repairs usually find at least one deviation from best practices. Some examples include no or partial TIP incision, single-layer urethroplasty, no barrier flap, single-stitch glansplasty or mattress suture glans wings approximation, and failure to check artificial erection after urethral plate transection.

For surgeons to optimally perform procedures, authors of articles and book chapters must describe key steps in precise detail so that readers can reproduce them.

Review Personal Results

Few surgeons know their personal results, instead assuming them to be similar to published outcomes or believing them to be low because they cannot recall the past patients they had with a problem like a fistula. The Dutch Hypospadias Study[3] suggests that both assumptions are often wrong. Similarly, we have found that nearly every time we review our results, they are not as good as we thought them to be.[18]

A simple chart review is sufficient to give an overview to a surgeon of his or her number of cases and complications. However, it is more efficient and accurate for individual surgeons to create a personal quality database using an Excel spreadsheet, and then maintain it prospectively. Information to be recorded includes patient name, date of surgery, primary or reoperative repair, technique used, date of follow-up, and complications (fistula, glans dehiscence, meatal stenosis, stricture, diverticulum, or recurrent VC). These data can be entered rapidly after surgery and postoperative clinic visits, and then reviewed periodically. Greater complications than the best published should then prompt a review of the surgeon's individual methodology to identify areas to improve. Review of subsequent patients confirms reduced complications.

We refer to this process as the three Ps: prospective data collection, periodic outcomes review, and practice changes to improve.[18] Other surgeons adopting this quality review have similarly told us that their results were not as good as they assumed, but improved once they realized the need to do better.

Specialized Proximal Hypospadias and Reoperations

Reviews of complex operations routinely find that the best results are achieved by high-volume surgeons. Certainly, the average of two proximal repairs done annually by U.S. pediatric urologists is not sufficient for the most complex forms of this condition, and likely explains, in part, the high complication rates reported by multiple centers.

There are only 1000 new male infants born in the United States with proximal hypospadias annually. There will only be approximately 1500 first-time complications each year (assuming 10% of distal and 50% of proximal repairs have a complication). While the complexity of reoperation varies, the fact that complications are greatly increased in patients undergoing reoperation suggests that these should also be considered high risk, similar to primary proximal repairs.

Therefore, we recommend that centers designate a single surgeon or surgical team to perform proximal repairs and reoperations, and then monitor their volume and results. Otherwise, few surgeons will have the volume needed to achieve and maintain expertise for these most challenging reconstructions.

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CHAPTER 74

Pediatric Urethral Trauma and Stricture

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INTRODUCTION

Urethral injuries in children are infrequent, accounting for 3.4% of children admitted with traumatic injuries of the genitourinary tract.[1] Significant morbidity may result from the impact on function and quality of life, with the need for specialized care and potential for multiple interventions. In general, the management of pediatric urethral trauma has followed treatment algorithms for adult urethral trauma.

ADULT VERSUS PEDIATRIC URETHRAL INJURY

Pediatric and adult urethral injury differ in several ways. Anatomic variation exists as the pediatric urethra is shorter, more mobile, and protected by an immature pubic bone. The bladder in a child is in a relatively intra-abdominal location compared with in the adult.

Pelvic fractures in children are more likely to be unstable and associated with a severely displaced prostatic urethra. Pediatric pelvic fractures occur with prostatic urethral displacement in 69%, whereas adult pelvic fractures are associated with a displaced prostatic urethra in 42%.[2] In children, concomitant bladder and urethral injuries occur in 20% of urethral injury, with coexisting anterior longitudinal urethral tears through the bladder neck and sphincteric complex. This is two times more likely to occur in children than in adults.[3] Similarly, in female children there is a higher likelihood that pelvic fractures have an associated urethral injury than in adult women.[4] Approximately 5% of pelvic fractures are associated with urethral injury, with higher rates of urethral injury in boys versus girls (7.4%–13.5% in boys and 4%–6% in girls).[5,6]

MALE URETHRAL INJURY

The male urethra can be divided into two segments, the anterior and posterior urethra. The anterior urethra includes the bulbar and pendulous (or penile) urethra. The posterior urethra includes the prostatic and membranous urethra, the latter of which is encompassed by the urogenital diaphragm. The pelvic floor separates the posterior and anterior urethra in both genders. The perineal membrane, which is the fascia of the urogenital diaphragm, signifies the extent of trauma as reflected by the amount of contrast extravasation above or below the urogenital membrane during a retrograde urethrogram.[7]

Classification of Urethral Injury

Anterior Urethral Injury

Anterior urethral injury in children is less common than posterior urethral injury.[8] It tends to result from blunt trauma, such as straddle injury to the perineum, occurring from a bicycle seat or crossbar, or from blows to the perineum from a fence or kick (Table 74.1). The bulbar urethra is most vulnerable to being damaged with straddle injury, representing the most common area of anterior urethral injury in boys (Figure 74.1).[9] The urethra gets compressed against the inferior aspect of the symphysis pubis. Straddle injuries do not typically occur with simultaneous pelvic fracture. However, blunt pelvic trauma with pubic rami fracture can occur in combination with bulbar urethral injury.

Posterior Urethral Injury

Posterior urethral injury is associated with pelvic fracture, tending to occur with motor vehicle collisions, crush injuries, and high-impact falls. The relative intra-abdominal location of a pediatric bladder and the more cranially placed prepubescent prostate predispose boys to complete posterior urethral disruption (Figure 74.2).[10] Prostatomembranous disruption occurs from major shearing forces at two fixation points of the posterior urethra. One point is the prostatomembranous junction, where the urogenital diaphragm is adherent to the ischiopubic rami. The second point is the fixation point of the prostatic urethra to the anterior pubic arch, the puboprostatic ligaments. The bladder and prostate are mobilized and displaced ("high-riding prostate") with this injury, with extraperitoneal urine leakage, and hematoma resulting from shearing of the dorsal venous complex (Figure 74.3a). The severe displacement of the pediatric prostate and nerve tissue disruption raise concern for future erectile dysfunction and incontinence.[11,12]

The risk of urethral injury occurring with a simultaneous pelvic fracture is directly related to the number of pubic rami fractures, degree of separation of the pubic symphysis, and presence of concurrent sacroiliac joint diastases.[13,14] Categories of fractures of the infant pelvis, according to Torode and Zieg, include types I, II, and III, which are stable fractures of avulsion, iliac wing fractures, and plain pelvic wing fractures, respectively.[15] Type IV fractures, also known as Malgaigne fractures, are anterior fractures through the rami or pubic symphysis coupled with posterior fractures of the ipsilateral ilium, sacrum, or sacroiliac joint, which typically occur from high-energy vertical forces transmitted to the pelvis via extended femurs. Malgaigne fractures carry the greatest risk of coexisting urethral injury (Figure 74.4).[16]

TABLE 74.1 Etiology of urethral injury

Condition	Cause
Anterior	
Blunt	Associated with straddle injury Falls Kick to perineum Horseback/bicycle riding Skateboarding/surfing
Penetrating	Gunshot wounds Impalement injury
Induced	Penile fracture Urethral foreign bodies
Iatrogenic	Urethral catheterization Circumcision Endoscopic evaluation
Posterior	
Blunt	Associated with pelvic fracture Motor vehicle accidents High-impact falls Crush injuries
Penetrating	Gunshot wounds Impalement injury
Induced	Urethral foreign body
Iatrogenic	Endoscopic evaluation Anorectal malformation repair

The Colapinto classification scheme defines posterior urethral injuries as determined with retrograde urethrography (Table 74.2). Type I injury is a stretched membranous urethra without rupture, type II injury is a complete rupture of the membranous urethra with an intact urogenital diaphragm, and type III is a membranous urethral rupture with urogenital diaphragm disruption.[17]

When a urethral injury and pelvic fracture are diagnosed concurrently, the risk of a coexisting rectal injury is present in 15% of children. While the role of pediatric digital rectal exam is controversial in accurately diagnosing a displaced prostate or rectal injury, it is recommended that radiographic and/or endoscopic modalities be used for rectal evaluation.[18] A missed rectal injury can result in significant morbidity, such as pelvic abscess, fistulization, osteomyelitis, and necrotizing fasciitis. When identified, rectal injury should be treated with temporary diverting colostomy.

DIAGNOSIS

Clinical Evaluation

Patients identified with pelvic fracture, straddle injury, or penetrating injury in the vicinity of the urethra should

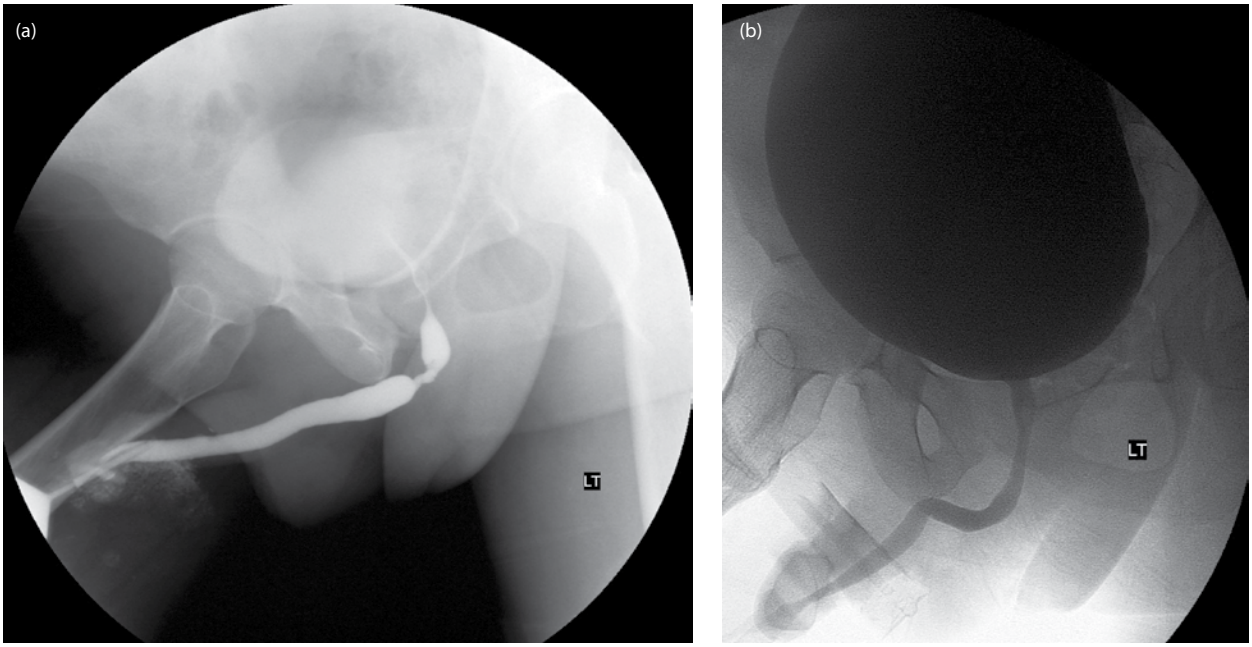

FIGURE 74.1 Radiographic images of a 16-year-old male with a bulbar urethral stricture that was a result of a straddle injury. (a) Preoperative retrograde urethrography demonstrates a 1.5 cm bulbar urethral stricture. (b) Six-month postoperative voiding cystourethrogram demonstrating the absence of the urethral stricture.

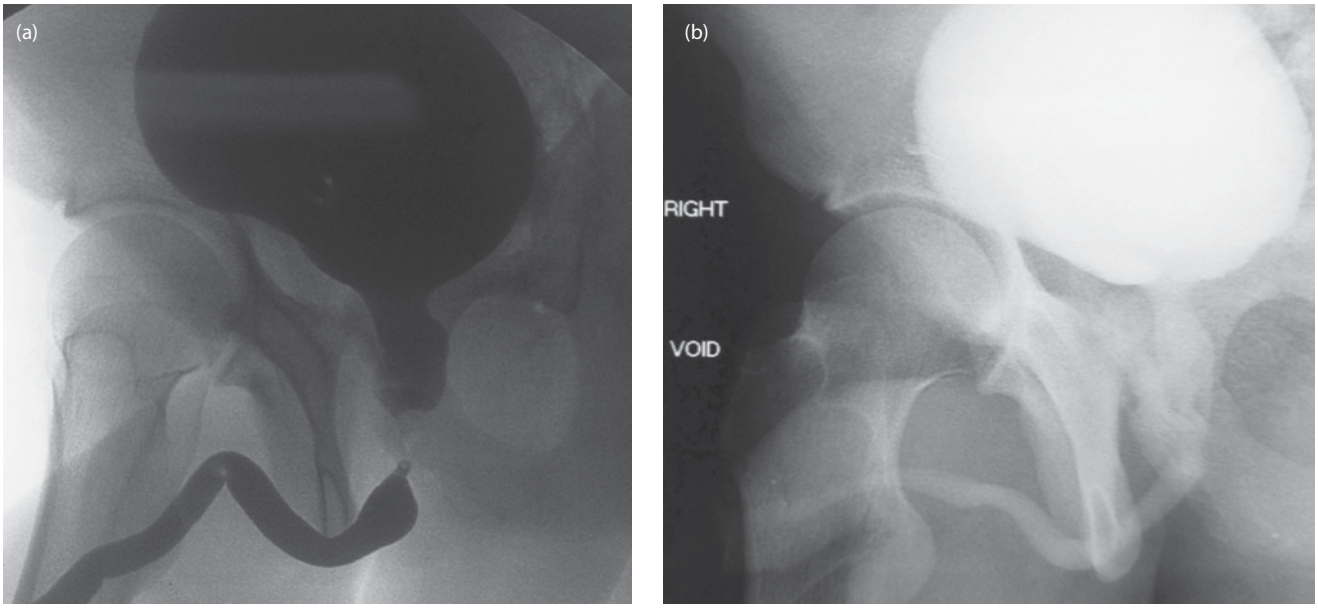

FIGURE 74.2 Radiographic images of a 15-year-old male who sustained posterior urethral disruption during a motor vehicle collision. (a) Simultaneous retrograde urethrogram and cystogram via a suprapubic tube delineate the urethral separation that has been filled in by scar. (b) Six-month postoperative retrograde urethrogram following posterior urethroplasty.

FIGURE 74.3 Urethral injury. (a) Posterior urethral injury proximal to the urogenital diaphragm with representation of leakage of fluid in the extraperitoneal pelvis and a high-riding prostate. (b) Anterior urethral injury distal to the urogenital diaphragm with leakage represented within the borders of Colles' fascia.

be evaluated for urethral injury. The classic findings that should raise concern for urethral injury include perineal, penile, labial, or scrotal hematoma; a palpable bladder; blood at the urethral meatus; hematuria; and inability to void.[19] Evaluation to rule out urethral injury should occur when there is pelvic fracture with a pubic rami fracture or symphyseal diastasis, or when radiographic findings suggest bladder neck injury. Injury of the anterior urethra, distal to the urogenital diaphragm, results in a characteristic "butterfly hematoma," which represents hematoma of

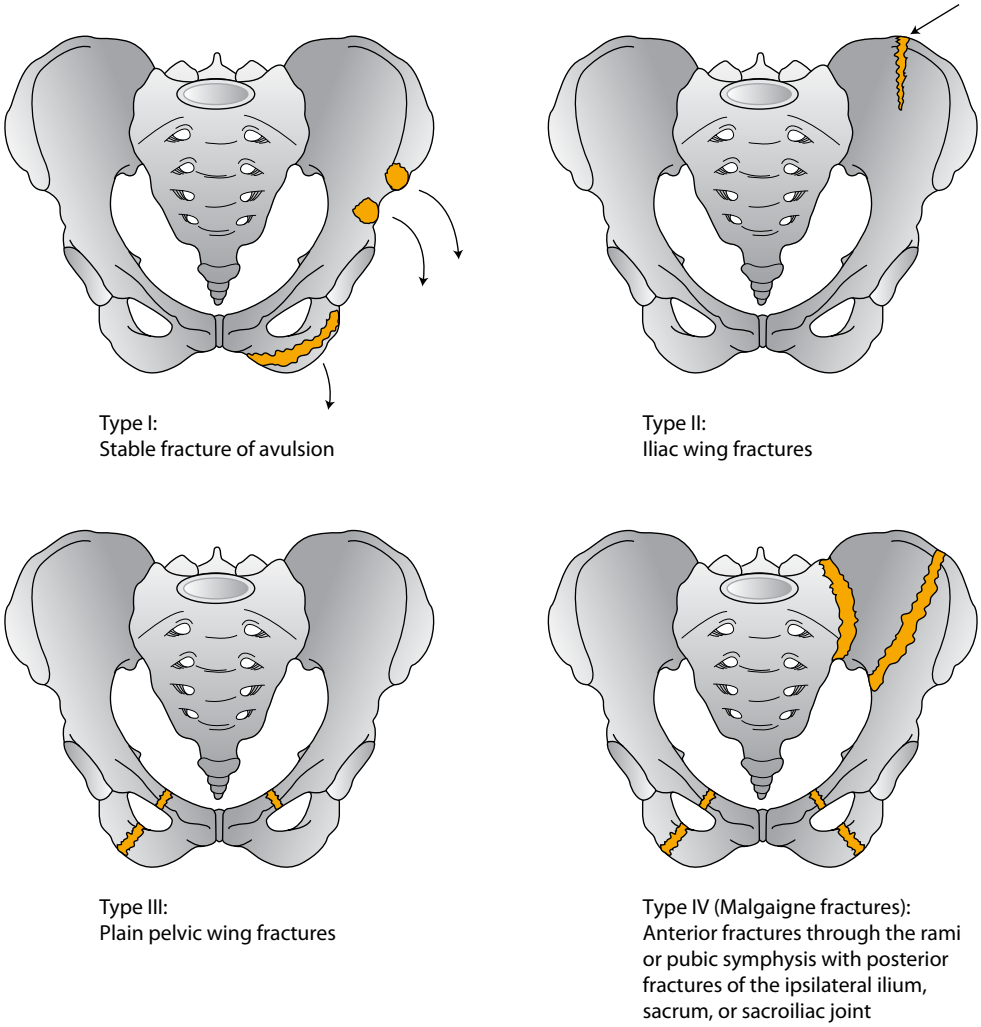

FIGURE 74.4 Torode and Zieg classification of fractures of the infant pelvis.

TABLE 74.2 Colapinto classification of posterior urethral injuries

Type	Description
Type I	Stretched membranous urethra without rupture
Type II	Complete rupture of the membranous urethra with an intact urogenital diaphragm
Type III	Membranous urethral rupture with urogenital diaphragm disruption

the superficial perineum that is contained by Colles' fascia (Figure 74.3b). Boys demonstrate scrotal enlargement from fluid extravasation through ruptured Scarpa's fascia, and its contiguous layer of the perineum, dartos fascia. Girls may exhibit labial swelling.

Radiographic Assessment

Significant lower genitourinary injuries were not found in stable pelvic fracture patients without gross hematuria, without multiple associated injuries, and with a normal genitourinary exam. Lower urinary tract radiographic evaluation of patients who fit these criteria may not be necessary.[1]

Retrograde Urethrography

Retrograde urethrography is considered the gold standard for the diagnosis of urethral injury, specifically male urethral injury. Proper technique includes patient positioning with the hips at an oblique angle, bottom leg bent, top leg straight, and the penis held on stretch. Scout imaging of the pelvis can demonstrate bony fractures of the pubic rami, pubic symphysis diastasis, and foreign bodies, including bullets and stones. A 6–8 French catheter is inserted into the fossa navicularis, and approximately 10 mL of undiluted contrast is injected transurethrally.

Computed Tomography

Urethral injury is typically associated with significant trauma; therefore, computed tomography (CT) scanning is the preferred initial radiographic modality to assess soft tissue injury, organs of the pelvis and retroperitoneum, and bony structures. While urethral injury is not always evident on CT, it does visualize the pelvic fracture and

associated hematoma. Radiographic literature suggests that CT provides an initial screening method for urethral injury, with a retrograde urethrogram to confirm male urethral injury and cystoscopy or vaginoscopy under anesthesia to confirm female urethral injury.[20]

Antegrade Urethrography

Posterior urethral injuries are typically managed by suprapubic tube urinary diversion. Antegrade urethrography via the suprapubic tube can be performed in conjunction with retrograde urethrography, to grade the extent and length of urethral injury or disruption and guide reconstructive planning.

Magnetic Resonance Imaging

MRI is generally reserved for the evaluation of urethral injury in preparing for delayed reconstruction, and is not typically used in the acute phase following injury. MRI can provide useful information about the location of the posterior urethral injury, length of the urethral obliteration, and degree of the external sphincter fibrosis.[21] While MRI offers the advantage of limited ionizing radiation versus CT, which is important in children, it does require the patient to be still. Therefore, sedation or general anesthesia may be required.

Cystoscopy

After suprapubic tube placement and radiographic demonstration of the urethral injury, cystoscopy may be performed to permit guidewire advancement into the bladder to facilitate primary urethral realignment. Due to the short female urethra, cystoscopic evaluation is noted to be of particular benefit.[22] Caution should be used in attempting cystourethroscopy in an injured pediatric urethra, especially without pediatric instruments and experience with pediatric urethroscopy, as manipulation may exacerbate the injury.

Preoperative Radiographic Evaluation of Urethral Stricture

The gold standard preoperative evaluation of a urethral stricture includes a combined retrograde and antegrade urethrogram to assess the length and location of the stricture and degree of stenosis. It is cautioned that the urethral defect that occurs after urethral distraction may be over- or underestimated by nonfilling of the fibrosed urethra distal to the verumontanum or by urinoma cavity formation that is in continuity with the end of the proximal segment.[23] Also, while Retrograde Urethrogram (RUG) can detect urethral stricture, it does not provide information on the extent of spongiosal fibrosis, which may bear significance in determining an operative plan. Therefore, it is recommended that urethrography be used in conjunction with other assessment tools, such as urethral ultrasonography.

Urethral Ultrasonography

Urethral ultrasonography is used intraoperatively at the case start to evaluate urethral stricture length and location, and provide details about spongiofibrosis that aid in deciding the optimal surgical approach. With retrograde saline instillation and a simultaneous suprapubic Crede maneuver, the urethral narrowing is evident adjacent to the distended urethra.[24] While the literature favors intraoperative urethral sonography for adult stricture assessment, reports show similar support for accurate measurement of adolescent anterior urethral stricture length and visualization of location.[25]

FEMALE URETHRAL INJURY

The female urethra develops to 4 cm in length, and pierces the urogenital diaphragm posterior to the pubic symphysis. It lies fixed against the anterior wall of the vagina, with a horseshoe-shaped, striated external urethral sphincter in the distal two-thirds of the urethra that fans out laterally along the inferior border of the pubic rami.

A high index of suspicion for urethral injury should occur in any female patient presenting with gross hematuria or blood at the introitus and a pelvic ring fracture. An estimated 40% of female urethral injuries are missed in diagnosis in the emergency department, with recommendation that proper assessment include adequate vaginal examination under anesthesia.[26] A delay may be required until pelvic fractures have stabilized, but a speculum exam and/or vaginoscopy should be performed, especially in the event of difficulty with urethral catheter placement.[27] While avulsion injuries are best diagnosed on physical exam or urethral catheterization, the best imaging modalities to aid the diagnosis of bladder neck or urethral injury include a CT cystogram and urethroscopy. Urethrography or voiding cystourethrography has been cited as less helpful.[22]

Female urethral injuries are typically associated with an unstable pelvic fracture. Disruption of the pubic symphysis occurs with a longitudinal laceration extending through the bladder neck and urethra, or by dislocation of a bony fragment that causes urethral laceration or transection. Urethroscopy and vaginoscopy are required for proper evaluation, and if clinically stable, it should be repaired. This includes primary bladder neck repair, end-to-end urethroplasty for distraction injuries, and longitudinal urethral lacerations repaired over a urethral catheter. Additionally, vaginal lacerations should be repaired, and a diverting colostomy should be performed for rectal injury. Delayed and multistaged approaches are associated with higher rates of failure, such as urinary incontinence, erosion, fistulization, or urethral obliteration. Approximately 30% of female pediatric patients with bladder neck or urethral injuries will need urinary diversion or continent catheterizable abdominal stomas secondary to high rates of complications.[3,28]

The female bladder neck is important for continence, and therefore should be repaired primarily via a transvesical approach and two-layer closure. Despite primary repair, variable rates of continence are reported in small series (48%–100%).[22,27] The midurethra should be closed primarily with a transvaginal approach and vaginal lacerations reapproximated over the urethra. This maintains urethral continuity, prevents urethrovaginal fistula, and prevents vaginal stenosis.[29] The distal urethra can be left hypospadiac, but some sutures may be needed for hemostasis.

Patients with female urethral injury are at risk for significant future sexual and lower urinary tract dysfunction.[27]

MANAGEMENT OF THE ACUTELY INJURED PEDIATRIC URETHRA

For suspected urethral injury, proper evaluation with urethral imaging, as earlier described, is necessary prior to attempting urethral instrumentation. To prevent infection that may occur from blood or urine extravasation, and accompanying inflammation, broad-spectrum antibiotics should be initiated. Additionally, urinary drainage should be established. In any trauma case, the patient needs to be stabilized, with priority given to treatment of life-threatening injury. In the acute setting, bladder drainage with suprapubic tube placement prevents ongoing urine extravasation and permits delayed urethral repair when the patient is regarded as ready. The goal of therapy, though, is to minimize the risk of fistulization (urethrocutaneous and vesicovaginal), periurethral diverticulae, stricture, incontinence, and impotence.

Generally, urethral repair may be performed immediately (within 3 days of injury) with primary realignment or primary sutured anastomosis, delayed (same modality done at 3–14 days postinjury), or performed late (more than 3 months following injury).

Posterior Urethral Injury

Controversy exists regarding the best method to initially treat posterior urethral injury. Most posterior urethral injuries are managed by suprapubic tube urinary diversion. Some advocate earlier repair at 7–10 days postinjury, while the periurethral and pelvic fibrosis is immature. The aim of earlier repair is not to prevent a stricture, but to make the developing stricture technically easier to treat.[30] However, for patients with more significant abdominal, pelvic, or life-threatening injuries, urethral repair can safely be postponed as needed. The completely disrupted bulboprostatic urethral segment will become scar through fibrosis.[31]

Primary open or endoscopic realignment attempts to bridge the disrupted urethral ends together using sounds or combination retrograde cystourethroscopy with guidewire advancement to reconnect the proximally displaced prostatic urethral stump. It has been shown to result in increased risk of impotence when compared with delayed repair (36% vs. 19%). This is believed to be related to periprostatic exploration and dissection.[32,33] Realignment may be particularly difficult in centers without sufficient pediatric endoscopic equipment.

Attempt at immediate repair of pediatric urethral disruption is cautioned against, given the associated high rates of complications, including stricture, restenosis, incontinence, and impotence.[34–36] Some suggest these complications result from the severity of the initial injury and not from surgical manipulation.[37]

Anterior Urethral Injury

For proximal anterior urethral injuries, stable patients can undergo primary endoscopic realignment over a guidewire. Alternatively, a suprapubic tube can be placed and assessment of the injury can be performed several weeks later by voiding cystourethrography. In the absence of urethral stricture or contrast extravasation, the suprapubic tube can be capped and subsequently removed if voiding is adequate. Immediate surgical repair can be performed for complete penetrating or open anterior urethral trauma that may occur with gunshot wounds or penile fracture; however, longer urethral defects or distracted ends require delayed reconstruction several months following the injury.[38]

Iatrogenic Urethral Injury

Iatrogenic pediatric urethral injury has been reported to occur with circumcision, urethral instrumentation, and repair of congenital anorectal malformation.[39] Potential injury from circumcision includes meatal injury, glans amputation with distal urethral injury, and development of urethrocutaneous fistula. Urethrocutaneous fistula can result from ischemic necrosis of the urethra, which can result from crush injuries by circumcision clamps, applied cautery, or sutures.[40] For injury sustained during urethral instrumentation, antibiotics should be administered along with urethral catheterization. Voiding cystourethrography can be performed between 1 and 3 weeks following the injury. Resulting strictures have traditionally been repaired when the child is over 1 year of age, given the concerns regarding general anesthesia. For children over the age of 1, waiting at least 3 months after injury provides sufficient urethral rest to permit stricture maturation.

The risk of urethral injury during repair of congenital anorectal formation is believed to occur when either no urethral catheter is placed during the rectal dissection or the urethral catheter is misplaced into the rectum via a rectourethral fistula. Accurate catheter placement with bladder drainage should be ensured before anomalous anatomical dissection is performed.[41]

Endoscopic Techniques

Popular in the late 1980s as a minimally invasive approach to treating obliterative posterior urethral strictures, the "cut-to-light" procedure combines retrograde and antegrade urethroscopy to open the urethra with knife incision or laser. Long-term stricture-free success is cited near 0%, with patients needing either daily catheterization to maintain luminal patency or urethroplasty. Therefore, the popularity of this procedure has diminished in favor of more durable approaches.[42]

Management of anterior urethral strictures is controversial in both pediatric and adult populations. Some reserve direct vision internal urethrotomy (DVIU) for short (<1 cm) nonobliterative anterior urethral strictures, claiming relatively high rates of stricture-free recurrence (75%–100%) following the procedure. Long-term follow-up shows stricture-free recurrence rates of 20%–35% at 5 years.[43,44] Others advocate initial DVIU regardless of preoperative stricture length, reserving urethroplasty for cases in which one endoscopic attempt has failed.[45] Endoscopic attempts may worsen the stricture severity, with more subsequent scar tissue and increased surgical difficulty.

Surgical success rates have been shown to decline with increased previous procedures.[46] Longer, denser strictures are likely better treated with open techniques.

Anastomotic Urethroplasty

In general, excision of the urethral stricture and primary anastomosis in pediatrics follows the same principles and steps as for adult urethroplasty. Anastomotic urethroplasty includes complete excision of scar tissue, widely spatulated urethral ends, and a tension-free anastomosis with urethral mucosal approximation. Typically, pediatric distraction injuries less than 2 cm can be performed in an end-to-end fashion, while urethral gaps of more than 3 cm will need adjunctive maneuvers to permit adequate anastomosis. Urethral mobilization distal to the penoscrotal junction risks penile shortening and chordee, so other techniques to aid in reducing tension on the urethral anastomosis include pubectomy, splitting or rerouting the penile crura, and a combination perineal and suprapubic approach. Since pediatric posterior urethral injury tends to occur with prostatic urethral displacement off of the pelvic floor, posterior urethroplasty in a child is more likely to need these maneuvers than adult urethroplasty.[47] Some advocate pediatric posterior urethroplasty with an initial transpubic approach.[10]

Using a mallet and osteotome, partial pubectomy permits access to the posterior urethra and bladder neck. Partial pubectomy has not been shown to affect bone growth, posture, or gait, and can safely be performed in children.[48–50] While it is rare to need total pubectomy in a child, close monitoring with periodic plain radiography can assess theoretical medial pubic bone regrowth, which risks impingement on the rerouted urethra. A reduction in the need for pubectomy may be related to improved visualization by use of high lithotomy positioning in candy-cane stirrups and use of a self-retaining ring retractor with flexible hooks.[51]

While coronal splitting has been described in pediatric urethroplasty,[52] select surgeons prefer not to split or reroute the pediatric urethra.[53] Controversy exists as to whether corporal spongiosal splitting procedures affect rates of erectile dysfunction.

Substitution Urethroplasty (Flaps, Grafts, and Multistage)

Traumatic pediatric urethral strictures greater than 3 cm in length are often approached in a single-stage flap procedure using prepucial or penile shaft skin (Orandi procedure and McAninch fasciocutaneous flap for long defects). Alternatively, if local skin is unavailable, a graft urethroplasty using a free skin flap or buccal mucosa can be performed.[47,54] Single-stage repairs involve opening the urethra on one side, where onlay placement of the graft or flap will permit maximal imbibition and inoscultation. For pendulous urethral strictures, dorsal onlay grafts are used, whereas bulbar urethral grafts can be placed either dorsally or ventrally. Ventral onlay bulbar urethroplasty avoids the need for lateral urethral dissection, is technically easier, and permits graft support from the thicker dorsally located bulbar spongiosum. However, a dorsal onlay bulbar urethroplasty may be preferred since it avoids incising the thicker area of the bulbar spongiosum. If the urethral defect is large enough that a flap or graft may need to be tubularized, the recommendation is to stage the procedure to reduce the risk of recurrent stricture. Staging the procedure by performing a classic two-stage Johansen urethroplasty or multistage flap or graft urethroplasty permits evaluation of graft survival, time for neovascularity, and assessment of the urethral plate for possible hair-bearing skin before urethral closure. Generally, urethral stricture length, the availability of well-vascularized excess adjacent skin, and the health of the donor bed determine single- or multistage approaches.

Bladder Neck Incompetence Following Posterior Urethral Injury

Urinary incontinence is a result of either concurrent bladder neck and urethral injury or damage to the pelvic or pudendal nerves with resultant sphincteric complex denervation.[38] Therefore, bladder neck injury should be fixed to restore urethral continuity. This is of fundamental importance to reduce the likelihood of urinary incontinence. If urinary incontinence results, an artificial urinary sphincter or bladder neck sling can be placed. However, with previous bladder neck reconstruction, artificial urinary sphincter placement risks urethral erosion. Artificial urinary sphincter mechanical life span is a further limitation for pediatric use. Alternative options include a continent catheterizable stoma with the Mitrofanoff principle, without an attempt to restore urethral continuity, or neourethral reconstruction using a bladder flap.[55]

Repair of Female Urethral Injury

Female urethral injury involves primary repair. Postponement of definitive repair in the female is believed to result in an obliterated urethra, and dense scar tissue of the anterior vagina that risks vaginal stenosis.[56] In combination with primary urethral repair, vaginal lacerations should be repaired.[57] For acute injuries so severe that there is an inability to identify or reapproximate urethral ends without tension, or with widely displaced pelvic fractures, suprapubic urinary drainage can be obtained with delayed definitive repair.[58] Approaches to repair include transvaginal, abdominal-vaginal, retropubic, or transpubic means.

For injuries associated with urethral loss as a result of pelvic fracture, neourethral reconstruction can be performed by tubularizing a segment of the bladder wall, in a manner similar to that of a Boari flap.[59] Delayed urethral reconstruction following complete urethral disruption after pelvic fracture has been associated with stress incontinence. In a small series of girls (median age of 6 years) treated with delayed retropubic urethroplasty with end-to-end anastomosis, 43% (3/7) demonstrated mild stress incontinence at a median 3 years' follow-up.[60] It is believed that the detrusor tone of the tubularized bladder flap contributes to continence, in addition to intraoperative bladder neck suspension.[61]

LONG-TERM FOLLOW-UP

Long-Term Follow-Up of Pediatric Urethral Strictures

There are limited published data reporting long-term outcomes of pediatric urethral stricture.

Rates of stricture recurrence have been reported to be the same at all anatomic levels of injury, with 39% of male pediatric patients with posterior urethral injury requiring a repeat surgery for urethral stricture recurrence and at a mean of 8 months following the initial surgery.[62] Urethral reconstruction using long-segment grafts or flaps may develop recurrent stricture, most commonly at the proximal or distal end of the urethral graft, or urethral diverticula. The recommendation is that the repair procedure should be individualized per patient, depending on the anatomy and extent of the urethral injury, patient stability, and presence of additional injuries.

Long-Term Functional Outcomes

Many reports on the long-term functional outcomes following urethral injury cite the injury itself as primarily responsible for the loss of potency and urinary symptoms.[63,64] Urinary incontinence is evident in 3.7%–20%, and erectile dysfunction is listed between 16.2% and 72%.[64] The evaluation of erectile function in a prepubescent male is limited, and requires long-term follow-up that is difficult to maintain with consistent data acquisition. Reports have shown that posttraumatic posterior urethral rupture in children poses risk to their psychological well-being. While nonoperative treatment of pediatric pelvic fractures with posterior urethral injury has been quite successful, repeated operations, the presence of long-term urologic complications, and frequent and long hospitalizations risk psychological harm. In one study of 49 children with posterior urethral disruption who were followed for a mean of 12 years (range 4–17) and an average age of 8 at the time of injury, development of psychological disease was more likely to occur with greater than three urologic procedures, the presence of long-term complications, and greater than three hospitalizations. Psychological disability occurred in 43% (dysthymic disorder, social phobia, posttraumatic stress disorder, anxiety, and depression). The authors recommend a multidisciplinary approach that includes physicians and mental health professionals for the treatment of these children.[65]

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CHAPTER 75

Abnormalities of the Penis and Scrotum*

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INTRODUCTION

Anomalies of the genitalia are common and, as a group, comprise the most frequent cause of birth defects in males. However, other than cryptorchidism and hypospadias, the majority of congenital malformations of the testis and scrotum are extremely rare and often associated with anomalies of other organ systems. Fortunately, most of these anomalies are identified at birth, and some are occasionally detected in utero.[1] Many other developmental abnormalities affecting the genitalia, such as patency of the processus vaginalis (hernia and/or hydrocele), varicocele, and the bell clapper deformity of testicular suspension, may not be apparent for many years but have the potential for significant long-term morbidity. For most genital defects, the etiology remains unknown. Congenital and acquired pediatric abnormalities of male genitalia, excluding intersex disorders, hypospadias, and cryptorchidism, are reviewed here.

NORMAL DEVELOPMENT OF THE PENIS AND SCROTUM

The external genitalia, including the genital tubercle and labioscrotal swellings, are indistinguishable in the male and female before the ninth week of human gestation.[2] The genital tubercle is formed by the migration of the mesodermal mesenchyme to the cranial portion of the cloacal membrane between the fourth and seventh weeks of gestation. Under the direction of the SRY gene and downstream processes, dihydrotestosterone causes subsequent development into the male phenotype in a proximal-to-distal fashion. The urethral groove deepens, and the urethral folds become distinct and then fuse in the midline. Recent work suggests that creation of the glanular urethra also occurs by fusion of the urethral plate, via the mechanism of epithelial–mesenchymal interaction, and not by the previously suggested ingrowth of surface glanular epithelium.[2–6] The paired labioscrotal swellings attain a more ventral position, either by actual migration or by relative change in position due to lengthening, and are anterior to the genital tubercle by 11 weeks of gestation. Fusion of the urethra up to the coronal sulcus is complete by 12 weeks. Developmental penile curvature is lost, and scrotal positioning is complete by 13 weeks. Fusion of the urethral folds within the glans proceeds as described for urethral closure in the shaft, and is accompanied by distal growth of the prepuce. By 24 weeks, the meatus is at the glans tip and the prepuce completely covers the glans, to which it is largely adherent.

PENILE ABNORMALITIES

Prepuce

Normal Development

At birth, the normal prepuce is usually unretractable because of physiologic adherence between the glans and inner preputial skin and/or tightness of the preputial ring. Ease of retractability of the prepuce increases with age, with complete retraction possible in at least two-thirds of 11- to 15-year-old and 95% of 16- to 17-year-old uncircumcised males.[7–10] Therefore, true phimosis is present in childhood only in cases of secondary fibrosis or balanitis xerotica obliterans of the prepuce, which occur in 0.8%–1.5% of uncircumcised boys.[11]

Circumcision

The prevalence of routine neonatal circumcision in the United States has dropped from close to 90% in the mid-1960s to an estimated 61.4% in 2002.[12,13] Epidemiologic data indicate that there are marked differences in circumcision rates based on socioeconomic class, ethnicity, and religious affiliation. The most recent American Academy of Pediatrics (AAP) Task Force on Circumcision report[14] stated that the risks of circumcision and now outweighed by the benefits of elective circumcision. However, the policy does state that the preventative benefits of circumcision are not enough to recommend routine elective circumcision in newborn males.

It is estimated that one in three uncircumcised men will experience a foreskin-related medical condition at least once in their lifetime.[15] In the most recent report, the AAP Task Force acknowledges potential medical benefits to

* Revised from MacDonald, M. F., Barthold, J. S., and Kass, E. J. Abnormalities of the penis and scrotum. In Docimo, S. G., Canning, D. A., and Khoury, A. E., eds., *The Kelalis–King–Belman Textbook of Clinical Pediatric Urology*, 5th ed. (Boca Raton, FL: CRC Press, 2007), 1239–70.

neonatal circumcision but concludes that these do not warrant its routine use. Benefits include reduction in the risk of urinary tract infection (UTI) in infant males and development of penile cancer as an adult. Data support an increase in the risk of symptomatic and asymptomatic UTI in uncircumcised male infants, probably because of an increased rate of periurethral and inner preputial bacterial colonization.[14,16] Similarly, penile cancer occurs almost exclusively in uncircumcised males. However, penile hygiene, including foreskin retraction with periodic cleansing, may also be preventative. Nevertheless, both of these conditions are rare, and their prevention by routine circumcision may not be justified. There is evidence that routine circumcision reduces the risk of acquisition and transmission of human immunodeficiency virus (HIV) in studies performed in underdeveloped countries.[17] The argument that the risk of sexually transmitted disease is reduced by circumcision is not supported by available data.[15,17,18]

Similarly, the risk of penile problems of sufficient severity to require circumcision is low.[8,14,11] Balanitis and balanoposthitis, characterized by erythema, edema, and purulent preputial discharge involving the glans and/or prepuce, occur in 3%–10% of uncircumcised boys. Paraphimosis, or retraction of a tight preputial ring with consequent severe glanular edema, is rare. Circumcision may be necessary only when these problems are severe or recurrent. However, even in these boys the use of topical steroids can significantly reduce the need for circumcision.[19] Since circumcision in older boys requires general anesthesia and may be associated with morbidity,[20] it should not be performed without discussing the option of medical therapy.

Newborn circumcision is performed with the Mogen or Gomco clamp or the Plastibell device.[21] Contraindications include hypospadias, chordee, penoscrotal fusion, buried penis, micropenis, and bleeding disorders. Complete separation of the prepuce from the glans with circumferential visualization of the corona is essential for adequate and safe newborn circumcision. Since significant physiologic response to pain has been documented in neonates undergoing circumcision, local anesthetic should be used.[14] Choice of anesthetic technique depends on the skills and experience of the surgeon, although penile ring block may be the easiest and most effective alternative.[22]

Older infants and children are circumcised under general anesthesia using a freehand sleeve resection technique with approximation of the penile shaft skin to the corona. Use of electrocautery in this technique has been deemed safe and effective for incision and hemostasis.[23,24] The choice of closure for freehand sleeve circumcision has traditionally been absorbable suture. Recently, 2-octyl cyanoacrylate (Dermabond) without the use of suture has become an option for closure of the shaft skin to the corona with good reported outcomes.[25,24] This technique avoids the irritation of the dissolving sutures and decreases the anesthetic time of the infants.

Complications of Circumcision

The risk of complications after circumcision is 0.2%–5%.[21] Bleeding is most common, occurring in 0.1% and more often in older boys, but is usually self-limited. Infection typically responds to local care but in rare cases may be associated with sepsis, necrotizing fasciitis, or death. Other complications of varying severity may occur, some of which may require further surgical intervention. Partial denudation of the penile shaft due to removal of an excess amount of skin will heal uneventfully with local wound care alone. Further intervention is required only to correct secondary chordee or phimosis. Conversely, excess or "redundant" preputial skin remaining after circumcision is often a source of concern for parents, but surgical intervention is rarely required. Resolution of physiologic adherence between the remaining skin and the glans will occur spontaneously after puberty, as in uncircumcised boys. Contracture of the healing edges of skin over the glans may produce secondary phimosis, also known as a trapped penis (Figure 75.1a). Correction requires excision of scar and, in some cases, penile skin flaps or Z-plasty for closure. Skin bridges (Figure 75.1b) between the shaft and glans may cause chordee and should be sharply incised. Inclusion cysts (Figure 75.1c) comprising retained subcutaneous epithelium should be completely excised. More severe injuries include glans amputation (Figure 75.1d), which can often be repaired acutely with success. However, subsequent meatal stenosis may require delayed urethroplasty.[26] Total penile necrosis (Figure 75.1e) is a rare but devastating complication of circumcision that is usually the result of using an electrocautery in combination with a metal clamp, such as a GOMCO. The use of electrocautery for circumcision is safe as long as it is not used in combination with a metal clamp.[23] Some investigators have recommended gender reassignment[27] for children with penile necrosis. However, male gender identity may be a consequence of testosterone imprinting, suggesting that gender conversion might be unsuccessful.[28] The decision of gender reassignment is difficult and should involve an experienced multidisciplinary team.[29]

Meatal stenosis occurs almost exclusively in circumcised boys. The proposed etiologies include frenular devascularization or chronic meatitis from exposure of the unprotected meatus to diaper irritation.[30,31] The incidence of symptomatic meatal stenosis after neonatal circumcision appears to be <10% based on limited available data, and possibly as high as 20% in asymptomatic patients.[32,30,33] Nonspecific symptoms, such as urethral bleeding, dysuria, or other voiding complaints, may be present, but the pathognomonic finding is upward deflection of the urinary stream as a consequence of an acquired ventral web (Figure 75.2).[34] Urinary tract imaging is unlikely to disclose significant pathology in the absence of incontinence or UTI. Meatoplasty or meatotomy can be performed under a brief general anesthetic or in the office after a generous application of EMLA cream.[35]

Defects of Number or Position

Penile Agenesis

Penile agenesis, or aphallia, is complete absence of the penis in an otherwise normal phenotypic and genotypic male (Figure 75.3).[36,37] Rudimentary erectile tissue is occasionally present. The estimated incidence is 1 in 10–30 million, and the presumed etiology absence or failed development of the genital tubercle. The majority

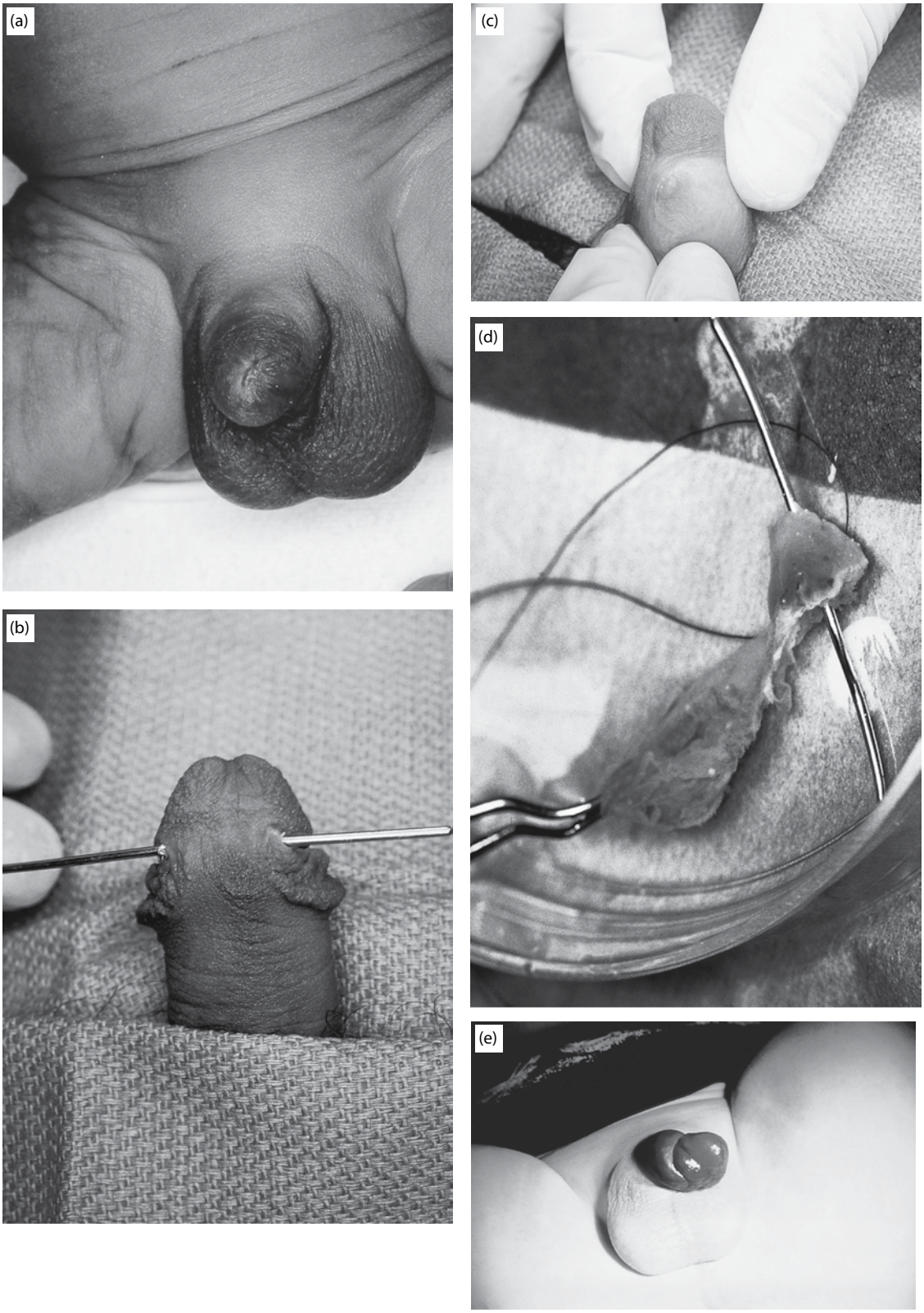

FIGURE 75.1 Complications of neonatal circumcision: (a) secondary phimosis; (b) skin bridge between glans and penile skin; (c) penile cyst; (d) glans amputation; (e) penile necrosis.

FIGURE 75.2 Upwardly deflected urinary stream in a boy with significant meatal web.

(54%) of patients have other genitourinary anomalies (e.g., cryptorchidism and renal and/or ureteral malformations) with or without gastrointestinal, musculoskeletal, and cardiovascular anomalies. Skoog and Belman[37] classified patients based on the relationship of the urethral meatus to the anal sphincter, noting increased additional anomalies and mortality with more proximal location of the meatus. The three variations that they described, in decreasing order of frequency, include postsphincteric with anterior perianal urethra, presphincteric with urethrorectal fistula, and urethral atresia with vesicorectal fistula. Treatment for these patients is controversial. Surgical intervention during infancy, including urethral transposition and bowel vaginoplasty via a posterior sagittal approach plus orchiectomy and scrotoplasty, has been advocated.[38,39] However, gender reassignment in other contexts and detailed psychosexual data may not support this recommendation.[29,36,37,40–45] In addition, since phallic reconstruction is feasible, however imperfect, in prepubertal boys,[46] maintenance of male gender should be considered an option in discussions with the patient's family.

FIGURE 75.3 Aphallia in a patient with a perianal urethral opening identified by sound.

Diphallia

Penile duplication or diphallia occurs in an estimated 1 in 5–6 million births.[47,48,49] The proposed etiology is branching or splitting of the genital tubercle soon after the fifth week of gestation. A balanced genetic translocation involving chromosomes 1 and 14 has been reported in one case.[50] Variants include partial and complete forms of true diphallia and bifid phallus. In the bifid variant, which is more common, the penis is branched at any point along its length, with each shaft containing a single corpus cavernosum. The designation of true diphallia is reserved for cases in which an accessory tricorporal penis (both cavernosa and spongiosum present), which may be hypoplastic, is present. The accessory organ may be located in the perineum or upper thigh. Ultrasound may be useful to characterize corporal anatomy.[47] Associated malformations are usually present and may include urethral duplication or agenesis, bladder duplication or exstrophy, hypospadias, epispadias, widened symphysis, cryptorchidism, and/or anorectal, renal, or scrotal anomalies. Also, cardiac and musculoskeletal anomalies have been reported.[51] Surgical repair involves excision of one completely duplicated penis or fusion of the bifid penis with urethral reconstruction.

Abnormal development

Penile Torsion

Rotational deformity of the penis (Figure 75.4a), usually in a counterclockwise direction, is most often associated with hypospadias and chordee but may occur as an isolated abnormality.[52] The incidence in a cohort of normal newborn males was 1.5%, with curvature of at least 90° seen in 0.7%.[53] Deviation of the median raphe without torsion was noted in 10% of newborns. Although a functional abnormality is absent if the penis is straight, penile torsion can be corrected in most cases by penile skin degloving and realignment. For more severe cases, this may be ineffective, and other procedures, such as a dorsal dartos flap rotation, may be utilized.[54,55]

Penoscrotal Fusion

Foreshortening of an otherwise normal ventral penile shaft occurs when the ventral penoscrotal junction is located distal to its normal position (Figure 75.4b).[56,57] This abnormality is called penoscrotal fusion or webbed penis, and may be congenital, due to removal of excess ventral skin during circumcision, or associated with hypospadias. Large, bilateral hydroceles in infancy may cause apparent penoscrotal fusion, which disappears with resolution of the hydrocele.[56] Lengthening of the ventral shaft

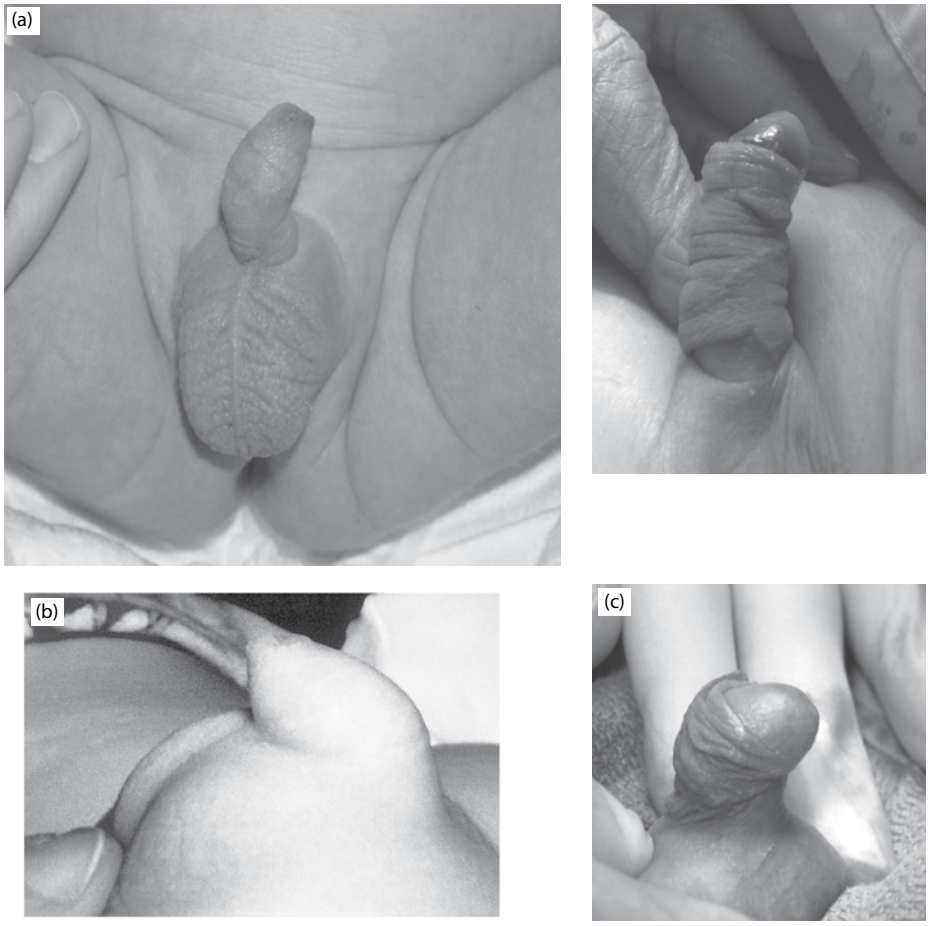

FIGURE 75.4 (a) Penile torsion, (b) Penoscrotal fusion, and (c) Chordee.

is most simply accomplished by preputial unfurling with or without ventral transfer of dorsal preputial skin. If the foreskin is not tight, use of the inner preputial skin for ventral shaft coverage during circumcision may be all that is necessary to correct the defect.

Chordee

Congenital chordee is a varying degree of curvature of the penis that is commonly observed in the presence of hypospadias (Figure 75.4c). It can be observed in 4%–10% of cases in the absence of hypospadias.[58] Ventral curvature is most commonly observed with the proposed mechanisms being related to skin chordee, fibrotic Buck's or dartos fascia, or in the case of lateral chordee, corporal disproportion.[59,60]

Assessment of curvature can be done at the time of repair by placing a fine-gauge needle into one of the corporal bodies and injecting saline to create an artificial erection. Standard repair was described by Nesbit in 1965, which involved degloving of the penis, excision of wedges from the tunica albuginea, and closure of these wedges in a vertical fashion in order to plicate the penis at the point of maximal curvature.[61] Anatomical studies have led to dorsal plication being performed in the twelve o'clock position in order to avoid the nerve fibers coursing along the penile shaft.[62] More recently, techniques using grafts and penile disassembly have been described.[58] However, these studies are small and lack long-term follow-up. For further discussion of chordee, refer to Chapter 73 on hypospadias.

Concealed Penis

An otherwise normal penis that appears to be small is called a concealed, buried, or inconspicuous penis (Figure 75.5).[63] Measurements of stretched penile length and penile diameter are normal. Etiologic factors include a prominent prepubic fat pad, generalized obesity, and/or poor fixation of the subcutaneous tissue of the penis to Buck's fascia. Most commonly, the patient is asymptomatic and spontaneous resolution can be anticipated with change in body habitus at puberty.[64,65] The extent of psychological distress in the untreated patient is unclear, and when surgical intervention is elected, results are poorly documented. Cromie et al.[63] reported prolonged (median 5 years) follow-up, with durable improvement in most cases using a preputial unfurling and degloving procedure similar to techniques used to correct penoscrotal fusion. Others have described simple anchoring of the penopubic skin to the prepubic deep fasica without degloving the penis, with good results.[66] However, the power of the study was low. The use of more complex procedures, such as prepubic liposuction or lipectomy, and closure with Z-plasties or skin flaps not only is rarely indicated but also may cause unnecessary scarring. Many reported early

FIGURE 75.5 Concealed penis in an obese prepubertal boy with normal stretched penile length.

failure in as many as 35% of cases, and long-term results are unknown.[64,67,68]

Micropenis

A penis that measures more than 2 or 2.5 standard deviations below the mean in stretched length for age, but is otherwise normally formed, is called a micropenis.[69,70] In newborns, a stretched length of less than 2.0 cm is considered abnormal. Normal development of the urethra and prepuce implies normal first-trimester development, with impaired penile growth occurring in the second and third trimesters. Cryptorchidism may also be present. The most common etiology is gonadotropin deficiency with or without panhypopituitarism.[69] Other endocrine causes include growth hormone deficiency, testicular dysgenesis or regression, and rarely, 5-alpha-reductase deficiency[298] or partial androgen insensitivity.[299] Micropenis may be present in gonadal determination disorders, such as Kleinfelter's syndrome and XX sex reversal, or in Prader–Willi, Lawrence–Moon–Biedl, Robinow, and other rare syndromes, or it may be idiopathic.[69,70]

Evaluation of patients generally includes karyotype; determination of serum glucose, serum electrolytes, cortisol, and growth hormone levels; and thyroid function tests and pituitary imaging as indicated.[69,70] Testicular function can be determined by measuring serum luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone before and after human chorionic gonadotropin (hCG) stimulation.[71] The dose of hCG is 500–1500 international units (approximately 3000 IU/m^2) every other day for 5–7 days, with serum testosterone measurements before and 24–48 hours after the last dose. Newborns can be evaluated for the normal spontaneous surge in serum gonadotropins and testosterone within the first few weeks of life; absence suggests a central (pituitary or hypothalamic) defect.

After diagnostic studies are complete, androgen stimulation therapy using intramuscular depot testosterone, 25 mg every 3–4 weeks for several months in infants, has been recommended to assess penile growth potential.[69,70] Unfortunately, response to testosterone does not always correlate with adequate penile size in adulthood, and may vary with the etiology of micropenis.[72,73] In this regard, patients with palpable testes[74] and significant response to gonadotropin-releasing hormone (GnRH) and hCG stimulation tests[75] appear more likely to have adequate long-term penile growth. Limited data suggest that treatment with dihydrotestosterone cream may be an effective alternative to parenteral testosterone, particularly in peripubertal males and in some patients who have failed testosterone therapy.[76] In patients with isolated growth hormone deficiency, growth hormone replacement appears to be sufficient for adequate penile growth.[77] Concerns that early androgen therapy might itself limit long-term penile growth potential are not supported by observations of males with early androgen excess syndromes.[78]

Until recently, routine gender reassignment was recommended for patients who showed no penile growth response to testosterone.[69,70] However, the advisability of routine gender reassignment in genetic males with functioning testes has been questioned in other contexts,[28,42–45] and the long-term results of reassignment for micropenis are not known. Adequate sexual functioning and clear male gender identity in adulthood have been reported in some patients raised as males with persistent small penile size in adulthood,[300] but not in others.[73] Additional long-term follow-up data are critically needed to facilitate clinical decision making in these patients. Therefore, gender reassignment should be performed with caution and should be accompanied by expert ongoing patient and family counseling, including a discussion of the risks and benefits of penile reconstruction.

Priapism

Priapism is defined as a prolonged, frequently painful penile erection not sustained by sexual activity. The most common pediatric cause is homozygous sickle cell (SS) disease, but other possible etiologies include other hemoglobinopathies, leukemia, local malignancy, viral infections, pelvic infections or appendicitis, trauma, diabetes, amyloidosis, and Fabry's disease.[79,80] Low-flow priapism (ischemic) is usually present in affected boys with sickle cell disease, while a high-flow state (nonischemic) is typically present in trauma-induced priapism, but may rarely also be present in sicklers.[81,301] The incidence of priapism in males with sickle cell disease is 2%–35%.[82–87,302] The pathophysiology has been thought to be vascular blockage caused by deformed red blood cells, but a component of endothelial inflammatory activation has also been suggested.[88] Stuttering episodes usually lasting less than 24 hours are common in both pediatric and adult patients. Initial episodes may occur in early childhood.

Priapism can be characterized by the site and degree of blood flow or stasis in the erectile tissues. Tumescence is usually limited to the corpora cavernosa but, in some cases, may also involve the corpus spongiosum, a situation termed tricorporeal priapism.[302] Spongiosal involvement, described in postpubertal individuals, is characterized

by a firm, tender, engorged glans. Voiding difficulty may occur in some patients. Studies used to characterize degree of blood flow include analysis of aspirated penile blood, technetium-99m (99mTc) penile flow studies, and color Doppler ultrasonography. However, appropriate radiological support is necessary to perform the latter two imaging studies.

Low-flow priapism is characterized by acidosis, hypercarbia, and hypoxemia on penile blood gas analysis. The usefulness and reliability of penile nuclear scans and Doppler studies in children remain unclear. Miller et al.[85] reported that nuclear scans did not predict outcome in a series of pediatric patients with sickle cell–associated priapism.

In the past, the initial treatment of patients with priapism due to sickle cell disease was hydration, analgesia, and transfusion to achieve a target hemoglobin S concentration of 30% or less.[82,83,85,303] However, in 2003 the Erectile Dysfunction Guideline Update Panel on the management of priapism[89] recommended that intracavernosal treatment should be administered concurrently with the above treatment if the priapism lasts longer than 4 hours. Intracavernosal therapy includes aspiration with irrigation and/or intracavernosal injection of a sympathomimetic drug. Prepubertal boys appear to respond more commonly to medical therapy than older patients.[84] Exchange transfusion has been associated with acute neurologic events characterized by reversible or irreversible cerebral ischemia, termed the ASPEN syndrome (association of sickle cell disease, priapism, exchange transfusion, and neurologic events).[304] Morbidity from this complication may be reduced by gradual or partial exchange transfusion, recognition of prodromal headache, and close monitoring.

With a total lack of response to medical and intracavernosal therapies, the next step should be surgical intervention.[82,85,87,89–91] The older view that surgical intervention in prepubertal patients with sickle cell priapism is unnecessary, if not contraindicated,[303] appears unjustified based on documented erectile dysfunction in boys following prolonged episodes of priapism.[90,92] For low-flow priapism, distal shunts (e.g., Winter, Ebbehoj, and Al-Ghorab procedures) should be attempted prior to proximal shunts (e.g., Quackels and Grayhack procedures), because the distal shunts have fewer complications and are easier to perform.[89,91] These usually produce detumescence. A modification to the Winter's shunt, using a large-bore needle with multiple punctures through the glans into the corpora cavernosa, has been suggested in the pediatric population with good postprocedure potency.[93] Available long-term follow-up data suggest that potency is more commonly preserved in prepubertal patients after episodes of shorter duration and when successful intervention occurs early.[90,94,95]

For the patient with high-flow priapism, diagnosed by history, corporeal aspiration, and blood gas analysis, the Erectile Dysfunction Guideline Update Panel on the management of priapism[89] recommends observation, along with ice packs and site-specific compression, as the initial management. High-flow priapism is not associated with ischemia and will often resolve without treatment.[96] Selective arterial embolization of the ruptured artery is the next step if observation fails or treatment is requested by the patient and/or family.[89,91]

A variety of other treatments have been suggested for patients with sickle cell disease and priapism; however, data are anecdotal or limited. Alpha-adrenergic agents such as etilefrine[97,98] have been given orally or intracavernosally with some success. Detumescence with hydroxyurea has been reported[99] but not confirmed in a large series. Other options include treatment with sildenafil,[100] GnRH analogues,[101] or antiandrogens,[102] but the latter two are not recommended in patients who have not achieved full sexual maturation and adult stature.[89]

Persistent, apparently painless penile erection has also been observed in newborns.[103] This condition resolves spontaneously in 2–6 days with no adverse sequelae. Associated, possibly contributing factors include polycythemia and birth trauma, although many reported cases are idiopathic.

SCROTAL ABNORMALITIES

Two main types of scrotal pathology occur in the pediatric population: the commonly observed acute swelling of a normal scrotum (discussed under the "Inguinoscrotal Disease" section) and the rare abnormalities of scrotal development.

Defects of Number or Position

Scrotal Agenesis

Complete absence of the scrotum is an extremely rare anomaly, with only six reported cases in the modern literature.[104–106,305] One case of hemiscrotal agenesis has also been reported.[305] Localized androgen insensitivity, localized 5-alpha-reductase deficiency, or labioscrotal fold formation failure have all been suggested etiologies for this condition.[305] The penis was normal in all the cases, the perineum was smooth with a median raphe present, and both testes were superior to the expected scrotal site. Successful repair using preputial skin was performed.

Accessory Scrotum

Ectopic scrotal tissue in addition to a normally developed scrotum is designated accessory scrotum or, in females, accessory labioscrotal fold. This anomaly is very rare, with just over 30 cases identified in the literature.[107,108] The accessory tissue is located on the perineum in the majority of cases and associated with a perineal lipoma and no other genitourinary anomalies. A case of isolated penile accessory scrotum has also been reported.[109] In the absence of a perineal lipoma, accessory perineal scrota are usually associated with other anomalies, including hypospadias, diphallia, defects of scrotal position, anorectal anomalies, and the VACTERL (vertebral, anal, cardiac, tracheoesophageal, renal, and limb anomalies) association.[306] Sule et al.[107] hypothesize that when present, the lipoma disrupts the continuity of the developing labioscrotal fold, and the etiology in other cases is generalized perineal maldevelopment.

Ectopic Scrotum

Ectopic positioning of the scrotum is usually unilateral, with the ectopic tissue usually suprainguinal but in

some cases infrainguinal (femoral) or on the thigh.[110–112] The ipsilateral testis is usually present within the ectopic hemiscrotum, although associated cryptorchidism has been reported. Ipsilateral renal and ureteral anomalies are common, so patients should be evaluated for upper tract anomalies. Associated skeletal defects, penile torsion or chordee, hypospadias, and cleft palate have also been reported. Chowdhary et al.[113] reported a case associated with a patent urachus. The etiology is uncertain, but may be related to a gubernacular defect failure of migration of the labioscrotal fold, or fetal deformation secondary to limb compression (foot). Treatment is generally simply achieved by flap scrotoplasty and orchidopexy.

Bifid Scrotum

Incomplete fusion of the labioscrotal folds may produce a partial or complete separation of otherwise normally positioned hemiscrota in patients with severe hypospadias or chordee. The defect may be corrected by excision of the abnormal tissue and creation of a new scrotal raphe with reapproximation of the hemiscrota in the midline.

Penoscrotal Transposition

In cases of penoscrotal transposition, part or all of the scrotum is located superior to the penile shaft. The spectrum of findings ranges from a normal-sized penis with confluent scrotal tissue both anterior and posterior (shawl or doughnut scrotum) to complete transposition of a rudimentary penis to the perineum behind an intact scrotum, a phenotype similar to that of penile agenesis.[114] The posterior aspect of the scrotum may be bifid and/or hypoplastic, and hypospadias and chordee are frequently present (Figure 75.6). However, multiple other anomalies of diverse organ systems have also been identified. These include renal, central nervous system (CNS), developmental, gastrointestinal, respiratory, limb, vertebral, cardiovascular, facial, and ocular anomalies.[114] Three types of chromosomal defects have been identified: trisomies 8 and 18, and distal deletions of the long arm of chromosome 13.[115] Correction of the defect may be performed during or subsequent to hypospadias repair by mobilization of the anteriorly placed scrotal skin with ventral transposition and closure, as described by Glenn and Anderson.[116] In some cases, ventral penile tethering may occur postoperatively that may be corrected by interposition of thigh-based neurovascular flaps.[117]

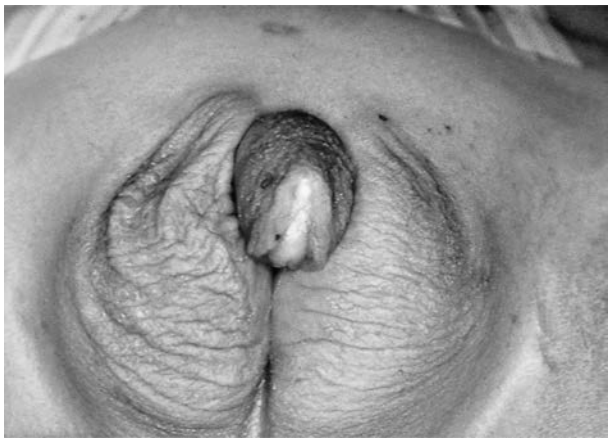

FIGURE 75.6 Partial penoscrotal transposition and bifid scrotum in a patient with proximal hypospadias.

Median Raphe Cysts

Midline cysts may arise anywhere along the median raphe between the urethral meatus and anus.[118,307,308] Their origin is believed to be epithelial or endothelial rests trapped in an aberrant subcutaneous location during developmental approximation of the urethral and genital folds. They may be large and elongated and appear translucent. Histologically, they are lined with cuboidal or squamous epithelium and contain sebacious material. Rarely, the proximal portion of the cyst may traverse the urogenital diaphragm and extend into the pelvis. Magnetic resonance imaging may be useful to define the extent of the lesion preoperatively if pelvic extension appears likely. Treatment is complete excision of the cysts with midline closure.

Inguinoscrotal Disease

Varicocele

Population studies have confirmed the observation that a varicocele first becomes clinically evident between the ages of 10 and 15 years,[309] and once a varicocele is present, it will normally persist for the remainder of that individual's life.[119] The varicocele that has its origin in adolescence may be a major cause of infertility in adults. However, if one waits until adulthood to treat varicocele-induced infertility, success is unlikely for the majority of men.[120] Because of this experience, recent efforts have focused on identifying teenagers with an asymptomatic varicocele in an attempt to identify individuals at risk, intervene earlier, and hopefully improve results. Although this approach seems reasonable, the problem for the clinician has been establishing uniform criteria for treatment. The observation that a varicocele occurs in 15% of men adds to the difficulties in deciding when treatment is indicated. Do we treat all men with a varicocele or just selected ones?

The vast majority of teenagers with a varicocele are discovered during a routine school physical, are asymptomatic, and are unaware of the presence of the varicocele. As a consequence, most of the teenagers identified with a varicocele have a grade II (mass or veins 1–2 cm in diameter) or grade III (large mass or veins easily visible and greater than 2 cm in diameter) varicocele. A child with a small varicocele (veins 1 cm or less in diameter) can only be detected by a skilled examiner, and most will escape early detection. No investigators have reported using color Doppler ultrasound to detect a subclinical varicocele in a teenager, and therefore this entity appears to have no clinical significance in the teenage population at the current time.

Since most teenagers with a varicocele are detected during a routine physical examination by a primary care physician, it is reasonable to assume that a teenager with a large varicocele is more likely to be diagnosed. Dubin and Amelar[121] concluded that the size of a varicocele was not a significant fertility variable. However, Fariss

et al.[122] and coworkers demonstrated that in adult men found to have a varicocele on routine physical examination, there was a greater chance of a man with a large varicocele having a sperm count of less than 20 million/mL than a man with a small varicocele. Several other studies have reported that in men with a large varicocele, there is greater impairment in semen parameters.[123,124,310] Steeno et al.[309] noted that with increasing varicocele size, there was progressively more volume loss of the testis ipsilateral to the varicocele. Other studies[311] have also demonstrated lower testicular volumes in men with a large varicocele than those with a small one. This loss of testicular volume may be significant because the seminiferous tubules comprise greater than 50% of the testicular mass, and in adult men, total sperm count correlates with testicular volume.[125,312] Therefore, it is reasonable to conclude that an individual with a large varicocele may be at greater risk for testicular injury.[126]

The mechanism by which a varicocele induces testicular injury is still unresolved, although many theories have been proposed. Investigators have also noted that a varicocele, both clinically and experimentally, results in an increase in scrotal and testicular temperature.[127] An increase in testicular temperature has been shown to be toxic to the testis in humans, as well as other mammals with scrotal testes.[128,129,313] Agger[130] reported that following varicocele correction, there was a good correlation between the fall in left testicular temperature and the improvement in spermatogenesis. Kass and Salisz[131] measured scrotal temperatures in adolescents with grade II and III varicoceles and reported that there was a significant bilateral elevation in scrotal temperature when compared with control subjects without a varicocele. They also noted that the higher the left scrotal temperature, the greater the volume loss of the left testis. Following successful varicocele correction, scrotal temperature normalized.

In an infertile adult male with a unilateral left varicocele, abnormal testicular histology can be demonstrated in both testes and involves all cell types, although the changes are typically more pronounced in the left testis (Figure 75.7).[132–134] Similar histopathology has been demonstrated bilaterally in the adolescent with a unilateral varicocele, but the abnormalities are less severe.[135,136] It is important to note that while the pathologic changes in the seminiferous tubules, blood vessels, and Sertoli cells are present to varying degrees in infertile men with a varicocele, the relative severity of the abnormality in these cell types is not the key prognostic variable. Investigators have reported that it is the severity of the Leydig cell pathology that is most significant in determining the potential for reversibility of the varicocele-induced testicular injury.[137] Luo et al.[138] showed apoptosis and suppression of StAR mRNA as the process through which Leydig cell injury occurred, which, in turn, caused a significant decrease in the intratesticular testosterone levels.[138] Individuals with Leydig cell hyperplasia have a very poor prognosis, while those with Leydig cell atrophy have a better prognosis for fertility following varicocele correction. The prognosis for return of fertility is independent of the degree of tubular pathology and more likely dependent on the pathologic changes in the Leydig–Sertoli cell interrelationship.[139] Hadziselimovic et al.[140] reported that Leydig cell atrophy was the predominant pathologic finding on testicular biopsy in teenagers undergoing varicocele surgery (74%) when compared with adults in whom Leydig cell hyperplasia was more common. These various histologic studies taken as a whole suggest that varicocele-induced histologic abnormalities occur in adolescents and are progressive. The pathology is potentially reversible early on, but once Leydig cell hyperplasia is present, surgical correction of the varicocele will be unlikely to have beneficial effects.

Varicoceles also induce endocrinologic abnormalities that parallel the histopathology. Weiss et al.[141] measured the in vitro synthesis of testosterone from testicular biopsy material and noted that there was a significant reduction in testosterone formation in 90% of infertile men with a varicocele. In these same individuals, peripheral levels of testosterone and LH were normal. Other investigators have also reported significant varicocele-induced Leydig cell dysfunction and noted that the abnormalities are progressive.[142,143,314] Furthermore, several studies show improved testosterone levels in adult men after varicocelectomy, possibly adding another indication for varicocele repair.[144,145]

An exaggerated gonadotropin response to the administration of GnRH has been demonstrated in infertile men with a varicocele and is thought to be the result of a primary testicular injury. The excessive release of LH following GnRH stimulation is an indicator of Leydig cell dysfunction, and the exaggerated FSH response is an indicator of an abnormality of the seminiferous tubules. Nagao et al.[146] measured the response to GnRH stimulation and noted that semen and hormonal abnormalities can be observed in both fertile and infertile men with a varicocele, suggesting that there may be some degree of testicular dysfunction in all men with a varicocele, regardless of their fertility status. They suggested that perhaps with increasing age, the varicocele-induced testicular injury could become clinically evident in more men. Several investigators[147–151] demonstrated that the excessive gonadotropin response to GnRH stimulation in infertile men was reversible after varicocele correction only in those individuals whose spermiograms also improved. Individuals who did not demonstrate an improved postoperative gonadotropin

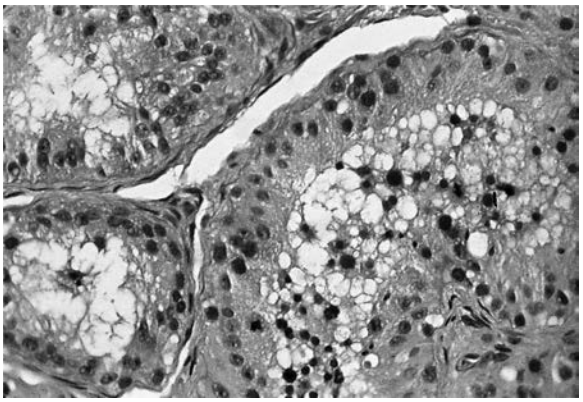

FIGURE 75.7 Testicular histology in a patient with a varicocele showing Sertoli only tubules and severe maturation arrest. Only 25% of tubules were normal in this patient (× 250).

response pattern did not show any improvement in their spermiogram.

The gonadotropin response to GnRH stimulation has been shown to be a useful diagnostic tool for evaluating testicular function in teenagers.[152,153] Kass et al.[154] measured the gonadotropin response pattern to GnRH stimulation in adolescent males with a varicocele and compared it with that of a group of normal teenagers without a varicocele. They noted that an abnormal gonadotropin response was present in almost one-third of teenagers with a varicocele, and that this test may be useful in identifying those varicocele patients with early evidence of testicular injury.

Barwell (1885)[155] was the first to report volume loss of the testis ipsilateral to a varicocele in a teenager, and noted that the testis "became harder and regained some of its dimensions" following surgical correction. In adult men with infertility, both testes tend to be smaller than those of aged-matched control groups without a varicocele. Kass and Belman[156] performed varicocele ligation on adolescent males with grade II or III left-sided varicocele and volume loss of the left testis. Significant catch-up growth of the left testis was noted in 80% of patients. Subsequent studies have confirmed their findings and indicate that a varicocele can be responsible for testicular growth retardation, and early successful correction can reverse this process.[157–160] In the majority of adolescents with a varicocele, testicular volume loss is the most common indication of testicular injury, and therefore the most significant indication for intervention. Normal testicular size correlates with stage of sexual maturity.[161,162] Testicular volume progressively increases from approximately 4 to 25 mL during pubertal development, making it difficult to calculate a normal testis volume in any individual before adulthood. A 20% volume loss on the ipsilateral side of the varicocele has traditionally been considered significant testicular volume loss (Figure 75.8). However, Li et al.[163] have shown that surgical intervention may reduce testicular hypotrophy for adolescent boys with a 10% size discrepancy. Fairly accurate testicular volume measurements are possible with a standard Prader orchidometer (Figure 75.9), but more accurate measurements may be possible with scrotal ultrasound using the Lambert (Length × Width × Height × 0.71) or Hansen (Length × Width × Height × 0.52) formula adjustments.[164] However, scrotal ultrasound is very dependent on the technician performing the study.

FIGURE 75.8 Left testicular volume loss in a patient with a left varicocele.

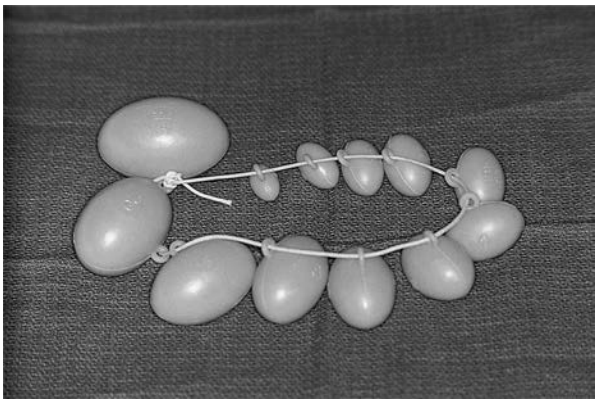

FIGURE 75.9 Prader orchidometer.

In adults with a varicocele, the assessment of a semen sample is a reasonable first step in the evaluation process since there are established normal parameters. Unfortunately, in adolescents it is often difficult to obtain such samples, and even when available, normal adult values for semen volume, spermatozoa concentration, and morphology are not achieved until 2–3 years after the onset of puberty.[165] It is important to remember that a single normal semen analysis does not predict future normality, since the effect of a varicocele may increase with time.[132] Although semen analysis is not practical in the adolescent population, at least one report has shown improvement in semen parameters after adolescent varicocele repair.[166] The establishment of normal semen analysis controls in the adolescent population and more routine use of this measure of the effects of varicocele could be useful in determining the need for surgical intervention. It is recommended that every adult with a palpable varicocele should have a semen analysis on an annual basis until the completion of his family in order to ensure that abnormalities do not develop.

Current data indicate that it is important to identify and evaluate all teenagers with a varicocele. Certainly no one can predict with absolute certainty whether any adolescent with a varicocele will be fertile or infertile; however, based on existing information, it can be expected that many will develop a fertility problem that becomes progressive if left untreated.[167–169] Individuals with volume loss of the testis ipsilateral to the varicocele appear to have a greater likelihood of having a normal semen analysis if treated as a teenager than if left untreated.[170,171,315] Similarly, individuals with large varicoceles may be at future risk for developing testicular volume loss and abnormal semen parameters. Although there are concerns that an abnormal GnRH stimulation test may be associated with similar long-term risks,[172] that hypothesis is not generally accepted as an indicator for intervention when other parameters are normal. Similarly, it is unclear whether intervention in otherwise normal individuals with bilaterally palpable varicoceles or scrotal discomfort is reasonable, and should be considered routine. Persistently abnormal semen parameters in older teenagers and adults are of significant concern and should be considered an indication for intervention.

Multiple techniques have been proposed for correction of a varicocele in a teenager.[173,174] Selective transvenous embolization of the internal spermatic vein[175–177,316] is a complex, invasive procedure with a significant recurrence and nonocclusion rate. Conventional inguinal[178] and retroperitoneal approaches with attempted preservation of the testicular artery are simple and relatively complication-free procedures but have an unacceptably high risk for failure.[179] Current data suggest that the above techniques are not the best choice for varicocele correction in teenagers. The Palomo technique,[180] with mass ligation of the internal spermatic vessels,[178,179,181–183,317] and the inguinal[184] or subinguinal approach,[185] with microscopic ligation[186–188] of all venous channels, are the procedures with the highest success rates and fewest complications, and are the procedures of choice for varicocele correction in teenagers. Secondary hydrocele may occur in 30% of patients undergoing mass ligation of the spermatic vessels, but only 5% of these patients require further surgical intervention.[189] Also, potential risk for testicular atrophy, should vasectomy be carried out in the future, must be considered. However, preservation of a single lymphatic vessel may prevent hydrocele. Laparoscopic ligation[190–194] of the spermatic vessels can also be done with good success (Video 75.1). This procedure requires intubation and bladder catheterization, and has the rare potential for significant intra-abdominal complications. However, the use of isosulfan blue injected into the scrotum can allow a lymphatic-sparing procedure to be performed, decreasing the hydrocele rate observed with the traditional Palomo varicocelectomy.[195]

Acute Scrotal Disease

Testicular torsion must be considered in any patient who complains of acute scrotal pain and swelling. Torsion of the testis is a surgical emergency because the likelihood of testicular salvage decreases as the duration of torsion increases. Conditions that may mimic testicular torsion, such as torsion of a testicular or epididymal appendage, epididymitis, trauma, hernia, hydrocele, varicocele, and Henoch–Schonlein purpura, generally do not require immediate surgical intervention. The cause of an acute scrotum can usually be established based on a careful history, a thorough physical examination, and appropriate diagnostic tests. The onset, character, and severity of symptoms must be determined. The physical examination includes inspection and palpation of the abdomen, testis, epididymis, scrotum, and inguinal region. Urinalysis should always be performed, and scrotal imaging is necessary when the diagnosis remains unclear.

History

The history and physical examination can significantly narrow the differential diagnosis of an acute scrotum. Testicular torsion is most common in neonates and postpubertal boys, although it can occur in males of any age. Henoch–Schonlein purpura and torsion of a testicular appendage typically occur in prepubertal boys, whereas epididymitis most often develops in postpubertal boys.

Testicular torsion usually begins abruptly in the early morning, and the pain is often severe from the onset. Moderate pain developing gradually over several hours or days is more suggestive of epididymitis or appendiceal torsion.

A history of scrotal trauma is common and does not exclude the diagnosis of testicular torsion. Minor scrotal trauma incurred during sports activities or rough, boisterous play typically causes severe pain of short duration. Pain that persists for more than 1 hour after scrotal trauma is not normal and merits investigation to rule out testicular rupture or acute torsion. Pain that resolves promptly after scrotal trauma only to recur gradually a few days later suggests traumatic epididymitis.

Many patients with testis torsion describe previous episodes of similar pain that lasted for only a short time and resolved spontaneously. Acute on-and-off pain associated with or without scrotal swelling suggests intermittent torsion with spontaneous detorsion. Voiding dysfunction, congenital genitourinary anomalies, and urethral instrumentation can predispose patients to bacterial UTIs and secondary epididymitis.

Physical Examination

A general abdominal examination should be performed, with particular attention given to flank tenderness and bladder distention. The inguinal regions should be examined for obvious hernias, swelling, or erythema. The spermatic cord in the groin may be tender in a patient with epididymitis, but typically is not tender in a patient with acute testicular torsion.

The scrotum should be assessed for discrepancies in size, degree of swelling, presence and location of erythema, thickening of the skin, and position of the testis. Unilateral swelling without skin changes suggests the presence of a hernia or hydrocele. A high-riding testis with an abnormal (transverse) lie may suggest torsion (Figure 75.10a), but this diagnosis is unlikely if the pain has been present for more than 12 hours and the scrotum has a normal appearance. In both epididymitis and testicular torsion, the affected hemiscrotum typically displays significant erythema and swelling after 24 hours.

The cremasteric reflex should always be assessed. One study[196] found that the cremasteric reflex was intact in 100% of boys aged 30 months to 12 years but was not consistently normal in infants and teenagers. The cremasteric reflex is rarely intact in patients with testicular torsion but is usually present in patients with torsion of a testicular or epididymal appendage.[318]

In early torsion, the entire testis is swollen and tender, and is larger than the unaffected testis. Tenderness limited to the upper pole suggests torsion of a testicular appendage, especially when a hard, tender nodule is palpable in this region. A small bluish discoloration representing the necrotic torsed appendage, known as the "blue dot sign," may be visible through the skin at the upper pole. This sign is virtually pathognomonic for appendiceal torsion when tenderness is also present. In early epididymitis, the epididymis exhibits tenderness and induration, but the testis itself is not tender. Swelling to the degree that the epididymis is no longer palpable can indicate testis torsion if the symptoms have been present for only a few hours. With both appendiceal torsion and epididymitis, loss of testicular

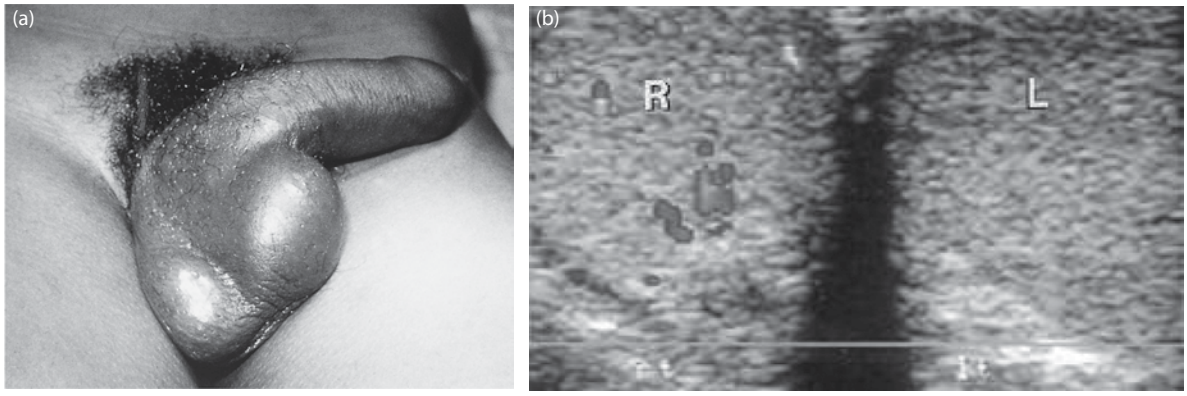

FIGURE 75.10 (a) High-riding, swollen left testis in a patient with acute spermatic cord torsion. (b) Ultrasound showing flow in right testicle and lack of flow in left testicle.

landmarks occurs later in the clinical course. The testis may be elevated to elicit Prehn's sign. Lack of pain relief (negative sign) may contribute to the diagnosis of testicular torsion. If torsion is suspected, manual detorsion can be attempted by rotating the testis away from the midline.

Diagnostic Studies

Urinalysis is performed to rule out UTI in any patient with an acute scrotum. Pyuria with or without bacteruria suggests infection and is consistent with epididymitis.

Historically, it was thought that no imaging studies were useful in confirming the cause of an acute scrotum. Immediate surgical exploration was thus the standard approach when torsion was suspected. However, studies conducted in the past few years have shown that only 16%–42% of boys with an acute scrotum have testicular torsion.[197–200] Therefore, routine exploration of all children is not reasonable if tests are available to improve diagnostic accuracy.

Initially, Doppler stethoscopes and conventional gray-scale ultrasonography were used to diagnose or exclude the presence of torsion, but these tests lack sensitivity and specificity.[201] Nuclear testicular flow studies are helpful, and when performed by experienced personnel, they can reliably identify children with torsion, epididymitis, and late torsion. However, since it is strictly a blood flow study, a testicular scan is not helpful when a hydrocele or hematoma is present because these conditions may mimic the findings of torsion. In addition, it is of critical importance to localize the exact position of the testis; otherwise, no reliable test is possible. In addition, most centers do not have personnel experienced in the performance or interpretation of nuclear medicine scrotal scans.

Color Doppler sonography has become the most popular diagnostic modality to evaluate a child with an acute scrotum because it is noninvasive and has a diagnostic accuracy at least equal to that of nuclear scanning. It can semiquantitatively characterize blood flow, distinguish intratesticular and scrotal wall flow, and also be used to assess other pathologic conditions involving the scrotum (Figure 75.10b).[202–204] Proper technique is essential. When color Doppler examinations are not performed correctly, false-positive or false-negative studies may occur. Certain caveats are important to remember. It may not be possible to demonstrate a Doppler signal in the small testes of very young boys. Just seeing color dots does not mean that flow is present; one must see a waveform within the substance of the testis. Reduced flow in a painful testis relative to the normal testis may indicate torsion, and exploration is indicated.

Spermatic Cord Torsion

The suggested protocol for the evaluation of a child with an acute scrotum (Figure 75.11) states that when the history and physical examination strongly suggest that testicular torsion is present and the duration of the pain is less than 12 hours, urgent surgical intervention is indicated.[205] With the widespread availability of color Doppler ultrasound, prompt triage and ultrasound can be performed without significant delay in treatment. When pain has been present for more than 12 hours or the diagnosis is unclear, ultrasound examination can be equally as helpful in making clinical decisions. It is important to remember that most patients with an acute scrotum do not have testicular torsion.

The "bell clapper" deformity is the underlying cause of testicular torsion in older children. In this deformity, the testicle lacks a normal attachment to the tunica vaginalis and therefore hangs freely. As a result, the spermatic cord can twist within the tunica vaginalis (intravaginal torsion).

Surgery is performed to correct torsion in the affected testis and to anchor the other testis to prevent future torsion. Surgical exploration can usually be accomplished through a single, small, midline incision in the scrotal raphe. Testes that are unequivocally necrotic should be removed. Viable testes should be fixed to the scrotal wall with multiple nonabsorbable sutures.

Testicular torsion can also occur perinatally before the entire testis complex has fused to the scrotum. In this type of torsion, the testis, spermatic cord, and tunica vaginalis twist en bloc (extravaginal torsion) (Figure 75.12). Clinically, extravaginal torsion generally appears as a hard asymptomatic intrascrotal swelling in the newborn. Erythema or a bluish discoloration of the scrotum is also frequently seen and may be confused with a hydrocele.

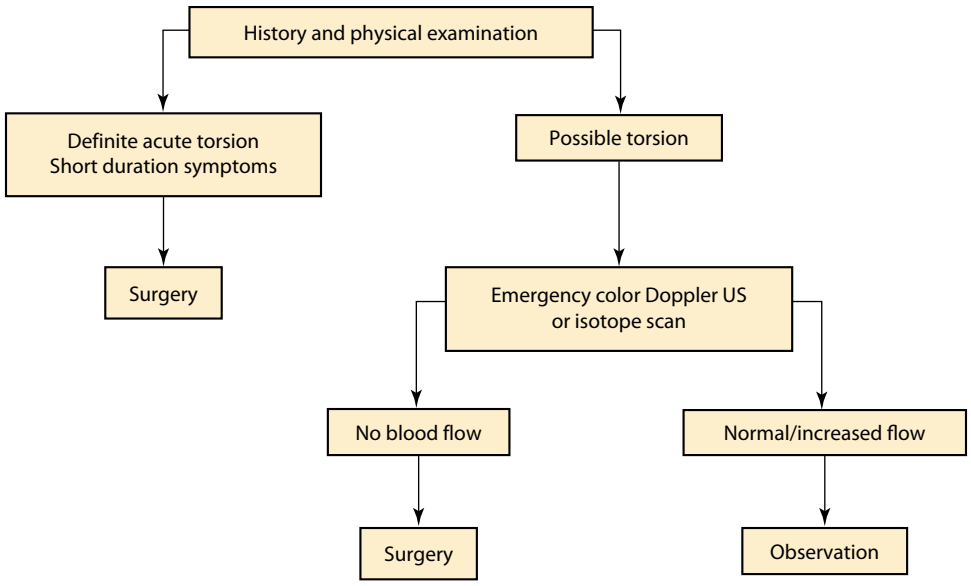

FIGURE 75.11 Algorithm for evaluation and treatment of patients with acute scrotal pain. (US = ultrasonography.)

The management of perinatal torsion remains controversial. Some surgeons advocate a nonoperative approach because of the poor potential for testicular salvage. Others argue that leaving a neonatal testis in place may have adverse effects on the contralateral testis and note that cases of bilateral neonatal torsion have been reported.[206] Also controversial is the question as to whether the remaining solitary testis should be fixed in place, although risk of torsion of that testis is no greater than that for the general (adult) population.

Torsion of an Appendix of the Testis or Epididymis

The appendix testis, a Mullerian duct remnant located at the superior pole of the testicle, is the most common appendage to undergo torsion (Figure 75.13). The epididymal appendix, located on the head of the epididymis, is a Wolffian duct remnant and may also become twisted. Torsion of either appendage produces pain similar to that experienced with testicular torsion, but the onset is more gradual. The cremasteric reflex is not lost with torsion of an appendage. Color Doppler ultrasonography often demonstrates increased blood flow that may be indistinguishable from epididymitis. Occasionally, a hypoechoic mass near the upper pole of the testis, the torsed appendage, may be visualized.

Torsion of a testicular appendage may be misinterpreted as epididymitis. However, if the urinalysis is

FIGURE 75.12 Extravaginal torsion (twisted cord – arrow).

FIGURE 75.13 Torsion of appendix testis (arrow). Note accompanying enlargement and hyperemia of the epididymis.

normal, no antibiotic therapy is required. Management entails symptomatic treatment to minimize inflammation and edema. Normal activity may both worsen and prolong the symptoms. Nonsteroidal anti-inflammatory drugs (NSAIDs) may offer symptomatic relief to some patients. The inflammation usually resolves within 1 week, although the testicular examination may not be completely normal for several weeks, with induration in the region of the head of the epididymis persisting for that interval.

Epididymitis or Orchitis

Epididymitis in adolescents and young adults is often unrelated to sexual activity and does not present with a UTI. In prepubertal boys, however, bacterial epididymitis is often associated with a urinary tract anomaly.[319] Any episode of epididymitis and UTI should be investigated with a renal bladder sonogram and a voiding cystourethrogram (VCUG) to rule out structural problems. However, the cause of epididymitis in the majority of young men can often not be determined.

Treatment includes empiric antibiotic therapy until the results of a urine culture are known. If the culture is negative, the symptoms are most likely to be due to abacterial chemical epididymitis caused by the retrograde reflux of urine into the vas deferens. Bed rest and scrotal elevation are often helpful. Symptoms may be alleviated with NSAIDs and analgesics. As with appendiceal torsion, the pain and swelling generally resolve within 1 week. Resolution of epididymal induration may require several weeks (Figure 75.14).

Scrotal Trauma

Severe testicular injury is uncommon and usually results from either a direct blow to the scrotum or a straddle injury. Damage generally occurs when the testis is forcefully compressed against the pubic bones. A spectrum of injuries may occur. Traumatic epididymitis is a noninfectious inflammatory condition that usually occurs within a few days of a blow to the testis.[207] Treatment is similar to that of nontraumatic abacterial epididymitis. Scrotal trauma can also result in intratesticular hematoma, hematocele, or laceration of the tunica albuginea (testicular rupture). Color Doppler ultrasonography is the imaging technique of choice (Figure 75.15). Testicular rupture is a surgical emergency requiring debridement of devascularized tissue and closure of the tunica albuginea. Isolated hematomas and hematoceles are managed on an individual basis.

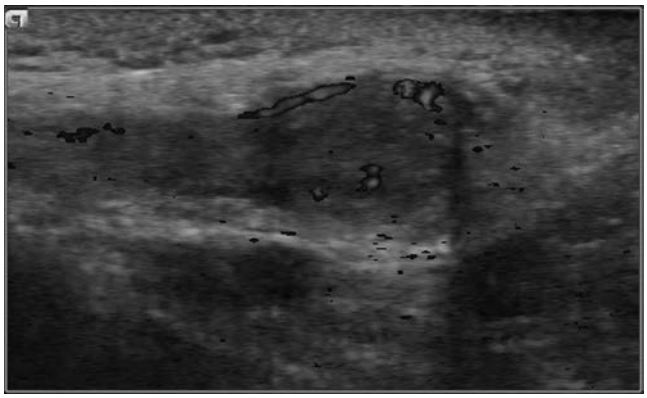

FIGURE 75.14 Epididymo-orchitis: Color Doppler ultrasound showing increased flow to a heterogeneous left testis and enlarged epididymis.

Lacerations of the scrotum itself are a fairly common occurrence in active boys, usually the consequence of bicycle accidents or getting caught on a fence. Most are superficial and do not involve the tunica vaginalis, requiring only minor suturing with sedation and local anesthesia. Deeper injuries may require a trip to the operating room.

Other Acute Scrotal Disease

Acute idiopathic scrotal edema is another cause of an acute scrotum (Figure 75.16). This condition is characterized by the rapid onset of significant edema without tenderness. Erythema may be present. It typically occurs in boys between the ages of 5 and 10, and can relapse in 20% of patients.[208] The patient is usually afebrile, and all diagnostic tests are negative. The etiology of this condition remains unclear. Treatment consists of bed rest and scrotal elevation. Analgesics are rarely needed.

Henoch–Schonlein purpura, a systemic vasculitic syndrome of uncertain etiology, is characterized by nonthrombocytopenic purpura, arthralgia, renal disease, abdominal pain, gastrointestinal bleeding, and occasionally, scrotal pain and swelling.[209] The onset can be acute or insidious. Hematuria may be present. The syndrome has no specific treatment.

The overriding need in the child with scrotal edema is to rule out testicular pathology. Color Doppler sonography may be helpful, but it may also be possible to make this determination clinically. If the testes can be manipulated gently into the superficial inguinal pouches and palpated, their noninvolvement in the inflammatory process may be proven and no further diagnostic studies need be carried out.

Hernia and Hydrocele

Inguinal hernia and hydrocele in childhood are most commonly due to patency of the processus vaginalis, an extension of the peritoneum that forms in the first trimester in proximity to the gubernaculum of both sexes.[210] In males, the processus vaginalis migrates distally through the inguinal canal with the masculinized gubernaculum, facilitates descent of the testes, persists distally as the tunica vaginalis, and normally becomes obliterated proximally. In females, the processus vaginalis develops but does not enlarge substantially. In both sexes, failure of closure of the processus creates a potential site for clinical hernia formation, characterized by passage of fluid or intra-abdominal viscera into the persisting sac.

The timing of closure of the processus vaginalis and its relationship to clinical hernia formation can be inferred from data obtained at autopsy, inguinal exploration, and intraoperative laparoscopy, and from studies of patients requiring ventriculoperitoneal shunts. These studies suggest that the processus is open in more than 80% of individuals at birth, and closure is most common in the

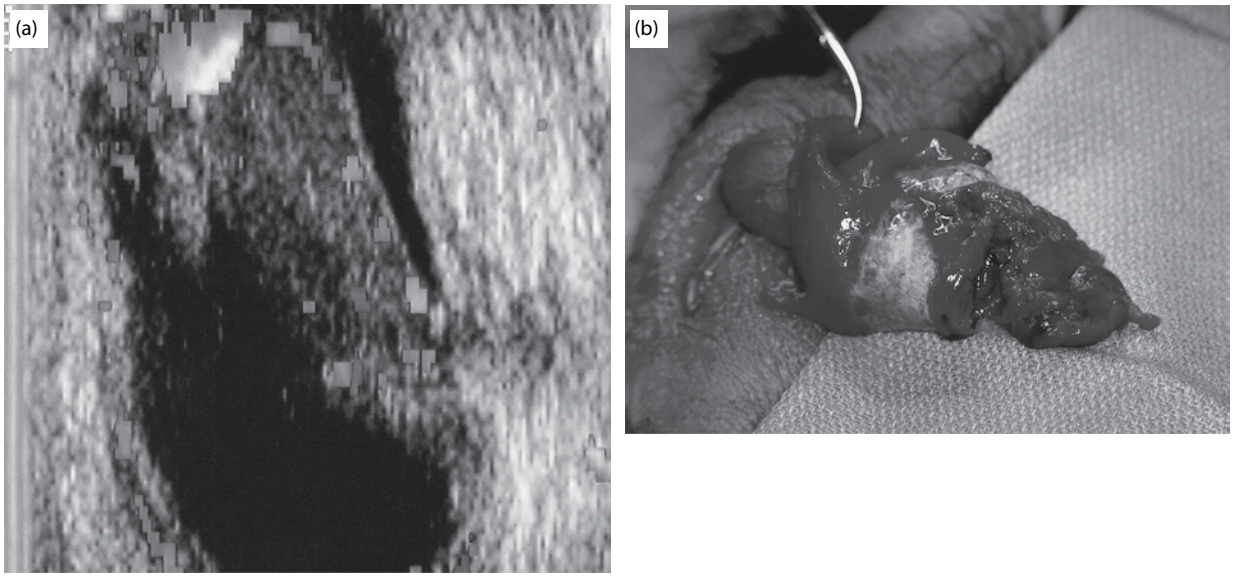

FIGURE 75.15 Testicular trauma: (a) color Doppler ultrasound showing discontinuity of testis and anechoic area at site of hematoma (asterisk); (b) intraoperative photograph showing disrupted testis with hematoma.

first year of life but may occur much later. Patency persists in 15%–30% of adults.[211,320] However, clinical hernias develop in fewer than 30% of newborns and 10% of 1-year-olds after placement of a ventriculoperitoneal shunt.[212] Similarly, contralateral patency of the processus vaginalis has been reported to be as high as 40%–50% of children with unilateral inguinal hernias.[213] However, only 7% of children who undergo unilateral hernia repair subsequently develop a clinical hernia on the opposite side.[214] Therefore, not all potential hernias manifest themselves clinically, even in the presence of increased intra-abdominal pressure.

FIGURE 75.16 Idiopathic scrotal edema.

The incidence of pediatric hernia is 10–20 per 1000 and is greater in premature infants (7%), in males (85% of total), and in the first 6 months of life (30% of total).[211,320] Clinical hernias are more frequent on the right side and are bilateral in approximately 10% of both male and female children. Incarceration occurs most frequently in the first year of life. Patients may present with an inguinal bulge and/or enlarged scrotum or labium, irritability, vomiting, and obstipation. In the absence of incarceration, a hernia may be diagnosed during the Valsalva maneuver (crying or blowing up a balloon) or by observation of inguinal asymmetry and palpable thickening of the spermatic cord distal to the external ring. These findings may be facilitated by examining the patient in the upright position. The spectrum of anatomic findings is shown in Figure 75.17.

Surgical repair is indicated when the clinical history and physical findings suggest visceral involvement or when fluctuation in size is observed. Prompt repair is also advised in infancy to reduce the risk of incarceration. If an incarcerated hernia requires reduction, surgical repair should be urgent, or emergent, if peritoneal signs suggest that bowel strangulation is present. The question of contralateral inguinal exploration at the time of repair of the symptomatic hernia is controversial. Some surgeons base their decision on laparoscopic evaluation of the contralateral internal ring.[213] However, while this may reduce the incidence of routine inguinal exploration, the data cited above suggest that the majority of patent processus vaginales will remain asymptomatic. Routine contralateral exploration may be reasonably limited to situations associated

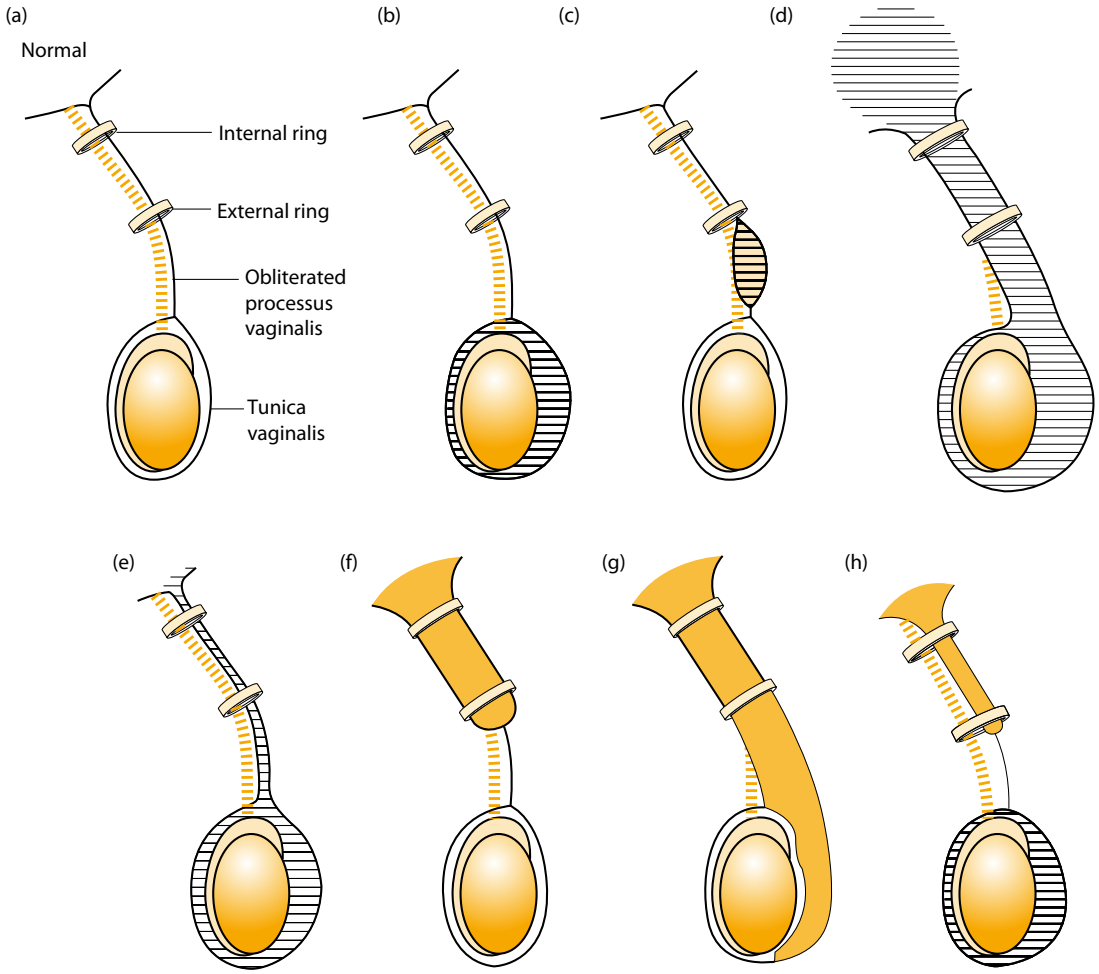

FIGURE 75.17 Possible findings in patients with hernia and/or hydrocele. Hatched black areas represent fluid and dark orange areas represent intra-abdominal contents: (a) normal findings; (b) scrotal hydrocele without hernia; (c) hydrocele of the cord; (d) abdominoscrotal hydrocele; (e) communicating hydrocele; (f) inguinal hernia; (g) inguinoscrotal hernia; (h) inguinal hernia and scrotal hydrocele.

with a higher risk for metachronous hernia and/or morbidity, such as age less than 1 year, history of prematurity, and increased abdominal pressure from shunts, dialysis, or ascites.

Principles of repair include a small, transverse incision over the inguinal canal, isolation of the sac with minimal handling of cord structures, reduction of any abdominal viscera, and high ligation of the hernia sac. Formal repair of the internal ring or floor of the canal is rarely needed in children. Generous windowing of an undrained hydrocele, which may be loculated, should be performed after transection and ligation of the hernia sac. The testis should be replaced in its normal position in the scrotum.

Scrotal hydroceles without associated patency of the processus vaginalis are common in newborns and may be quite large. Diagnosis is made by transillumination, and the inability to reduce the mass, forcing the fluid back into the peritoneal cavity, rules out hernia. Most resolve spontaneously, and treatment is not recommended.

Persistence of a simple scrotal hydrocele beyond 18 months of age may be an indication for surgical correction. However, there is no evidence that a simple hydrocele risks testicular damage. Treatment is generally cosmetic, although some boys will complain of discomfort if the mass is particularly large.

Fluid may also be trapped within the tunica vaginalis of the spermatic cord. The diagnosis is made by identifying a nondecompressible, transilluminatable mass above and separate from the testis.

Treatment of simple hydroceles or hydroceles of the cord is similar to that in adults; however, an inguinal approach is recommended to rule out associated patency of the proximal tunica vaginalis at the level of the internal inguinal ring. Excision or plication of the enlarged tunica vaginalis is generally effective.[215]

Finally, hydroceles may occur acutely following minor scrotal trauma or a viral illness associated with coughing or vomiting. The acute rise in intra-abdominal pressure associated with coughing or vomiting may force peritoneal fluid through a minimally patent processus vaginalis. Many of these will resolve spontaneously, and a period of observation for several weeks before recommending surgical intervention is advised.

Many unusual structures have been observed within hernia sacs:[216]

- Abscess
- Adrenal hemorrhage
- Adrenal tissue and adrenal tumor
- Appendix
- Bladder
- Dystic dysplasia of testis
- Dermoid cyst
- Ectopic renal tissue
- Ectopic testis
- Epidermoid cyst of testis
- Epididymal cysts, nodules, structural anomalies, and tumors
- Fat necrosis of scrotum
- Fibrous adnexal pseudotumor
- Free nodules and calculi
- Funniculitis (thrombosis of pampiniform plexus)
- Gonad or genital structure of opposite sex
- Granulomas (talc, etc.)
- Glaucomatous disease (acidosis, etc.)
- Hemangioma
- Intussuscepted processus vaginalis
- Lymphangioma
- Meckel's diverticulum (Littre's hernia)
- Meconium granuloma
- Mesenchymoma
- Neuroblastoma
- Parasitic disease
- Paratesticular cyst
- Paratesticular rhabdomyosarcoma
- Pedunculated body
- Peritonitis pseudotorsion
- Pneumoscrotum
- Polyarteritis nodosa
- Polyorchidism
- Richter's hernia
- Scrotal calculi
- Spermatic cord tumors
- Spermatocele
- Splenogonadal fusion
- Testicular infarct
- Tunica albuginea cyst
- Tunica vaginalis tumor
- Ureter
- Uterus
- Vas deferens agenesis
- Vasitis nodosa
- Venous thrombosis
- Wilms' tumor
- Xanthogranuloma (juvenile)

Preoperative clinical findings will suggest the presence of some of these structures, such as spermatic cord tumors. Previously unsuspected discoveries in the inguinal canal become clinically significant in the context of hernia repair if they suggest an additional diagnosis that requires treatment, are confused with normal tissue, or are removed inadvertently, producing morbidity. Additional diagnoses of significance include persistent Mullerian duct syndrome (usually associated with cryptorchidism), Meckel's diverticulum, intersex abnormalities in phenotypic females, and testicular, vasal, or epididymal anomalies (see below). Since androgen insensitivity syndrome is present in about 1% of girls undergoing hernia repair,[217] routine exposure of the ovary and/or vaginal examination under anesthesia is warranted in these cases.

Incompletely developed portions of vas or epididymis have been identified by microscopic analysis of excised hernia sac tissue in 1.5%–4% of cases and may cause concern of vasal injury. These can be differentiated from normal vas and epididymis by their small mean diameter of 0.17–0.26 mm, versus >0.7 mm for normal ducts.[218,321] Serious injury to the normal vas, bladder, ureter, or testis during hernia or hydrocele repair is uncommon (2%).[57,211,219] Even in the subset of boys requiring hernia repair in infancy for incarceration, the rate of testicular atrophy is low[321] (2%). Hernia recurrence is also rare (<0.5%). Postoperative (new or persistent) hydrocele may be found in 1.5%–3.5% of cases, but the majority resolve spontaneously within 1 year.

A more severe and unusual form of hydrocele is the abdominoscrotal hydrocele (ASH), which extends from the scrotum to the retroperitoneum but has no demonstrable communication with the peritoneal cavity.[220,221,322] Presentation is usually unilateral but may be bilateral. Bimanual examination confirms an abdominoscrotal mass that transmits a fluid wave; ultrasound may be useful to confirm the diagnosis in some cases. Often present at birth, the ASH may become quite large, extending laterally to the level of the umbilicus or higher. They often do not regress and may enlarge with time. They may rarely cause pain, lower extremity edema, hydronephrosis, and testicular atrophy.[221,222]

Proposed etiologies include isolated closure of the processus vaginalis at the internal ring with gradual upward extension of the hydrocele retroperitoneally, or incomplete proximal obliteration of the processus producing a one-way valve mechanism with continued accumulation of fluid.[220,322] Associated undescended testis may be present. ASH repair is generally performed through a standard inguinal incision, although imbrication of the wall transcrotally may be safer.[223] The sac is transected, the distal portion opened widely, and the retroperitoneal portion excised completely to prevent recurrence. Extreme care must be taken to avoid injury to local retroperitoneal structures, such as the vas or ureter, which may be difficult to identify in the folds of the large hydrocele wall.[322] For this reason, the scrotal approach may be preferable. Concomitant orchidopexy is performed, if indicated.

Testicular Abnormalities

Congenital testicular anomalies other than cryptorchidism are rare but are often found in association with abnormal testicular descent. Those associated with intersex disorders are reviewed elsewhere (see Chapter 70).

Defects of Number and Position

Anorchism and Monorchism

The absence of one or both testes in otherwise normal phenotypic males is identified in as many as 35% of patients

evaluated for nonpalpable testes.[224–226] In the majority, the vas and spermatic vessels are present but end blindly distal to the internal inguinal ring, a condition called vanishing testis. Several observations indicate that the likely cause of vanishing testis is antenatal torsion. These include the presence of hemosiderin or calcification in 15%–85% of specimens examined histologically,[224–226] the absence of developmental abnormalities in the contralateral testis,[227] and sonographic confirmation of prenatal testicular disappearance in a patient with extravaginal torsion.[228] The diagnosis of anorchism can be made after the first 3 months of age if both elevation of plasma gonadotropins and lack of testosterone response to hCG stimulation are present.[229] However, testosterone levels are elevated until about 2 months of age in the normal male. Therefore, the absence of measurable levels in this age group suggests anorchia. During mid-childhood, gonadotropin levels may be normal in anorchid boys, but a GnRH stimulation test will reveal an exaggerated gonadotropin response. Contralateral testicular enlargement and elevated FSH levels are present in some, but not all, patients with monorchism.[230,231] Therefore, diagnosis must be based on laparoscopic and/or surgical findings of blind-ending spermatic vessels. Reduced levels of serum Mullerian inhibiting substance may also prove useful in the diagnosis of anorchism.[232]

Polyorchidism

Supernumerary testis is a rare entity, with fewer than 100 case reports in the literature.[233–236] The proposed etiology is complete duplication of the genital ridge or separation of the ridge into two or more parts. The extra testis is most commonly located in the scrotum (75%), but may be inguinal (20%) or retroperitoneal (5%). The condition is rarely bilateral (5%). Associated ductal structures on the affected side may be single or duplicated. The anatomic variants described in the literature include shared epididymis and vas (47%), duplicated epididymis and common vas (33%), duplicated epididymis and vas (11%), and the absence of both adjacent to the accessory testis (5%). Associated genital anomalies are common and, in decreasing order of frequency, include inguinal hernia, undescended orthotopic testis, spermatic cord torsion, hydrocele, testicular tumor, and varicocele. The diagnosis is suspected by physical findings and can often be confirmed sonographically (Figure 75.18). Surgical intervention is indicated for torsion, hernia or hydrocele, suspected tumor, or cryptorchidism.

Testicular Exstrophy

Congenital extrusion of one or both testes outside the scrotum is one of the rarest testicular anomalies.[237,238] There are inadequate data to support any specific etiology, but theories include gubernacular malfunction, scrotal ischemia, or local mesodermal abnormality. No associated anomalies are reported. Treatment is simple scrotal orchidopexy and closure.

Transverse Testicular Ectopia

The presence of both testes on the same side, each with an intact ipsilateral blood supply, epididymis, and vas, is an uncommon malformation.[239,240] A fused vas deferens has also been reported in four cases in the literature.[241] The most frequent associated anomalies include inguinal hernia (98%) and persistent Mullerian duct syndrome (30%). The absence of a normal attachment of the gubernacular remnant suggests that anomalous development of this structure may predispose to transverse ectopy. Laparoscopy may be useful for both diagnosis and management.[242–245] Depending on presentation, orchiectomy or orchidopexy is performed with partial excision of Mullerian remnants as required to facilitate scrotal placement of the testis.

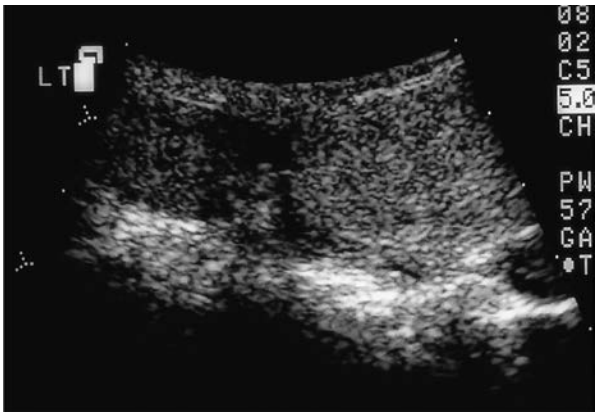

FIGURE 75.18 Polyorchidism: ultrasound image showing two normal testes on the left side.

Other Testicular Anomalies

Gonadal Fusion Anomalies

Splenogonadal fusion is a rare anomaly characterized by an abnormal attachment between the left gonad or its internal ductal system and the spleen or accessory splenic tissue.[246–249] Almost 150 cases have been reported, with the majority occurring in males. Patients most commonly present with a scrotal mass, inguinal hernia, or undescended testis. Rare presentations include bowel obstruction, ambiguous genitalia, and acute enlargement or traumatic rupture of the scrotal spleen. Two variants are described: a continuous form characterized by a fibrous connection between the gonad and spleen, which may contain accessory "spleenlets," and a discontinuous form, with no connection between the gonad and the orthotopic spleen. These subtypes occur with similar frequency. Other congenital anomalies are present in about one-third of cases, including limb, skull, or cardiac defects; micrognathia; diaphragmatic hernia; imperforate anus; spina bifida; and hypospadias. Proposed etiologies include adhesion between splenic and gonadal tissue at 5–9 weeks' gestation due to simple fusion or inflammation[246] and migration of splenic cells into a persistent diaphragmatic gonadal ligament.[248] Treatment is based on associated findings, but care should be taken to avoid injury to the associated normal testis.[246]

Two cases of hepatogonadal fusion have appeared in the literature.[250,251] One patient presented with a right

inguinal hernia, and had a histologically proven liver nodule attached to the upper testicular pole with a fibrous attachment to the porta hepatis. No other anomalies were present. The second patient had a fibrous cord-like structure containing hepatic tissue along its length connecting the liver and right testis in a patient undergoing right inguinal hernia repair.

Testicular Hypertrophy and Macroorchidism

Testicular volume is usually less than 2 mL prior to puberty.[252,323] After the age of 9–10 years, testicular size is markedly variable but correlates with Tanner stage.[323] Unilateral or bilateral enlargement of the testis has many etiologies. Malignant lesions, including primary testicular tumors and leukemia, are rare but should be ruled out initially. Benign causes of increased testicular size include asymmetric pubertal enlargement,[253,254] compensatory hypertrophy in some cases of monorchism or cryptorchidism,[255] macroorchidism associated with fragile X and other mental retardation syndromes,[256,324] nodular enlargement in patients with congenital adrenal hyperplasia,[325] and isosexual precocity due to CNS lesions, excess gonadotropins, testotoxicosis, hypothyroidism, and other syndromes.[257]

Testicular size discrepancy at puberty in otherwise normal boys is an uncommon finding. If a history of previous inguinal surgery or testicular injury is absent, the proposed cause is asymmetric response of the testis to normal maturational stimulation.[254] Exaggerated bilateral, benign testicular enlargement is also reported.[253] These patients should be evaluated with testicular sonography, and if a tumor is not identified, no further steps are indicated. Over time, the size discrepancy in unilateral cases may persist or resolve.[254]

Microlithiasis

Microlithiasis is a condition usually reported in adult men, but also found in children.[258] It is characterized by ultrasonic and/or histologic evidence of multiple calcifications within the testicular parenchyma (Figure 75.19).[326] Adult men with microlithiasis often present with other testicular disease, and associated germ cell tumors have been reported in as many as 40%.[259] By contrast, the prevalence of microlithiasis in men who have had testicular sonography for other reasons is 0.6%.[260] However, recent studies have failed to show the suggested link between microlithiasis and increased cancer risk.[261] The exact incidence in the general population is unknown, but a study of 1504 young asymptomatic men 10–35 years old found a 5.6% prevalence of testicular microlithiasis.[262] A study by Wasniewska et al.[263] revealed a high prevalence of testicular microlithiasis in males with McCune–Albright syndrome.

Microlithiasis identified by pathological examination is not always evident by sonography. However, the histologic type may be helpful in determining the significance of the lesion.[326] Hematoxylin bodies are associated with germ cell tumors, while laminated calcifications may be present in association with testis tumors but also occur in normal boys and in other diseases affecting the testis, including cryptorchidism, epididymitis, inguinal hernia, and Kleinfelter's syndrome.

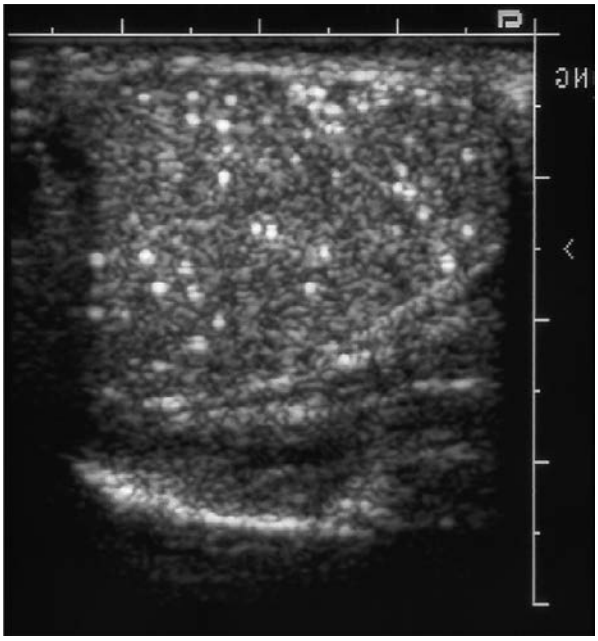

FIGURE 75.19 Testicular microlithiasis: typical appearance on ultrasound image.

Histological microlithiasis is even rarer in the pediatric population, identified in only 1 of 2100 autopsies and 1 of 600 testicular biopsies.[264] In a multi-institutional series, Furness et al.[258] studied 26 patients aged 6 months to 21 years (mean 12 years) in whom microlithiasis was diagnosed incidentally by sonogram. Reasons for evaluation included hydrocele, epididymitis, varicocele, trauma, testicular or appendix torsion, testicular mass, and unilateral testicular enlargement. There were no cases of clinically evident tumor during a mean follow-up period of slightly more than 2 years. Additionally, long-term data are required to identify the clinical significance, if any, of testicular microlithiasis in children. For the present, the subject of surveillance of these patients is controversial. In the abscence of risk factors such as history of testicular tumor or cryptorchidism, some would only recommend self-examination.[261] Others advocate evaluation every 6 months with examination and ultrasound, but do not recommend routine biopsy.[265]

Abnormalities of Accessory Organs

Cystic Dysplasia of Rete Testis

Cystic dysplasia of the rete testis (also called cystic dysplasia of the testis) has been reported 48 times in the literature.[266–269] This lesion is believed to be due to a defect in fusion between the rete testis and efferent ducts. Cystic dysplasia is usually unilateral but may be bilateral, and patients often present in childhood with a testicular or scrotal mass. The diagnosis may be made by identifying multiple small cysts on the medial aspect of the testis, although most of the testicular parenchyma may be compressed by the mass. Associated genitourinary anomalies

are common, suggesting that an associated Wolffian duct anomaly may be present. Almost all cases are associated with renal anomalies. The most common are agenesis, dysplasia or hypoplasia, or hydronephrosis. Abdominal cryptorchidism is seen in one-third of patients. Preferred treatment is local excision, but an inguinal approach with control of the cord vessels is recommended to rule out tumor. Orchiectomy is preformed if testis sparing is not possible. Some advocate a more conservative approach with serial ultrasonography.[269,270]

Wolffian Duct System

Since the mesonephric or Wolffian duct is the precursor of both the ureteral bud and the internal genital ducts, including vas, epididymis, and seminal vesicles, anomalous development frequently affects both the kidney and reproductive tract.[271] The caudal segment of the Wolffian duct, or common mesonephric duct, is the site of the origin of the ureteral bud. The middle segment, or common vas precursor, becomes the vas and seminal vesicles, and the upper mesonephric duct becomes the distal vas and epididymis.[272] It is proposed that defects that appear before the seventh week of gestation (onset of ureteral bud differentiation) may interfere with normal renal and reproductive tract development, and after that time, the reproductive tract alone is affected.[271] The timing and extent of the development defect probably influence the eventual phenotype.

Agenesis

Absence of the vas deferens is the most common finding in patients with agenesis of Wolffian duct derivatives.[271,273–275] The lesion may be bilateral or unilateral and, in either form, occurs in less than 1% of males. Vasal agenesis is usually discovered in adult patients with infertility or at the time of planned vasectomy, but may also present during inguinal exploration at any age. Both the unilateral and bilateral forms are associated with agenesis of the epididymis, seminal vesicle, and/or kidney, but the association is more frequent in unilateral cases. The caput epididymis almost always persists. This observation supports other clinical data indicating similarities between the caput epididymis and the efferent ducts, with the implication that the caput arises from the gonadal ridge rather than the Wolffian duct. Mutation of the transmembrane conductance regulator (CFTR) gene is the only known genetic etiology of vasal agenesis. CFTR gene mutations are more common in bilateral (64%) than unilateral (25%) disease and have not been found in patients with bilateral vasal agenesis in association with renal anomalies.[271] When vasal agenesis is diagnosed in childhood, renal and pelvic sonography and, if abnormal, VCUG should be preformed. Vasal agenesis may be found in patients with cystic fibrosis, even when clinical evidence of the disease is absent.

Anomalies of Epididymal Attachment

Abnormalities of fusion or suspension of the epididymis are known to be common in patients with cryptorchidism. Turek et al.[276] studied epididymal anatomy in a group of boys undergoing inguinal or scrotal exploration primarily for hydrocele and reported normal anatomy in 96%. However, two other studies have shown a higher incidence (31%–39%) of mild suspension or fusion anomalies of the epididymis in boys with hernia or hydrocele, with a greater frequency in those patients with a patent processus vaginalis.[277,278] The clinical significance of partial epididymal detachment or a long looping epididymis in patients with a normally positioned testis is unclear.

Epididymal Cysts

Cysts of the epididymis (spermatocele) (Figure 75.20) usually appear during puberty or adulthood and are asymptomatic. The etiology is unknown, but proposed theories include dilated efferent ducts that have failed to fuse with the epididymis[271,279] and/or part of a testicular dysgenesis syndrome caused by an endocrine abnormality.[280,281] Conditions associated with a higher incidence of epididymal cysts include cryptorchidism, von Hippel–Lindau disease, and fetal exposure to diethylstilbestrol. Intervention is not usually required, but both excision[282] and sclerotherapy[283,284] have been used successfully in symptomatic patients. Two cases of torsion of an epididymal cyst have been reported.[285]

Other Vasal Anomalies

Ectopy of the vas deferens,[272,286,287] also called persisting mesonephric duct,[327] is characterized by ectopic insertion of the vas into the urinary tract. Most commonly, fusion of the vas and ureter occurs proximal to the bladder (vasoureteric insertion),[288] but direct entry of the vas into the bladder (vasovesical insertion) may occur. Approximately 30 cases are reported in the English literature. Ectopic insertion into a prostatic utricle is also possible (Figure 75.21).

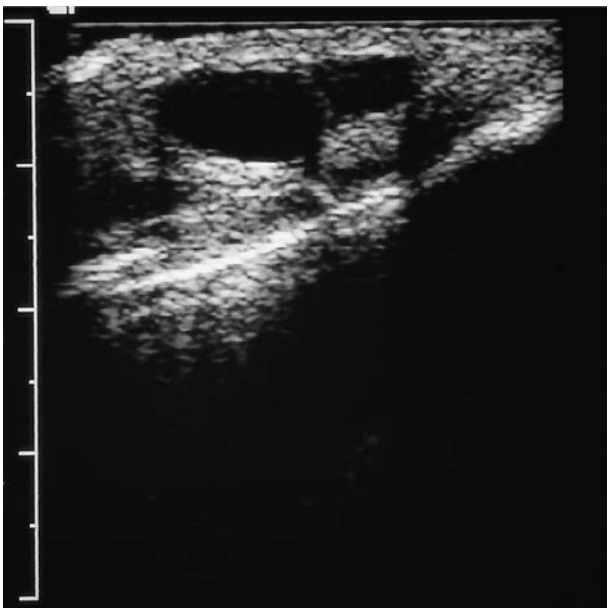

FIGURE 75.20 Epididymal cysts in a patient with polyorchidism.

FIGURE 75.21 VCUG of patient with prostatic utricle showing insertion of vas deferens into utricle.

Proposed mechanisms include ectopic insertion of the ureteral bud and/or aberrant development of the proximal vas precursor.[272,327] Patients are asymptomatic or present with UTIs and/or epididymitis. Other congenital anomalies are common, including agenesis of the seminal vesicles, imperforate anus, hypospadias, ureteral reflux and/or ectopy, and renal anomalies. The triad of imperforate anus, hypospadias, and ectopic vas was reported in 21% of cases.[289] The diagnosis may be made by cystourethrography or retrograde ureterography, or at the time of ureteroneocystostomy. Treatment is based on anatomic findings and clinical indications.

True duplication of the vas deferens is extremely rare. Binderow et al.[290] reported a single case found at the time of inguinal hernia repair in a boy with a normal urinary tract. The authors proposed Wolffian duct duplication or ductal bifurcation in the region of the proximal vas precursor as the etiology.

Seminal Vesicle Cysts

Seminal vesicle cysts are another rare manifestation of anomalous Wolffian duct development.[291,292,328] They may be congenital or acquired.[293] Most are associated with renal agenesis with or without ureteral ectopy. Presentation is predominantly in adulthood, with pain during micturition, defecation or ejaculation, UTI, or infertility. A palpable mass is appreciated on rectal examination. The diagnosis may be confirmed by abdominal or transrectal sonogram. A computed topographic scan may be useful to visualize the seminal vesicle and confirm renal agenesis (Figure 75.22). Excision is indicated in symptomatic patients, either using an open technique, such as a transtrigonal approach,[292] or laparoscopically or robotically.[294–296]

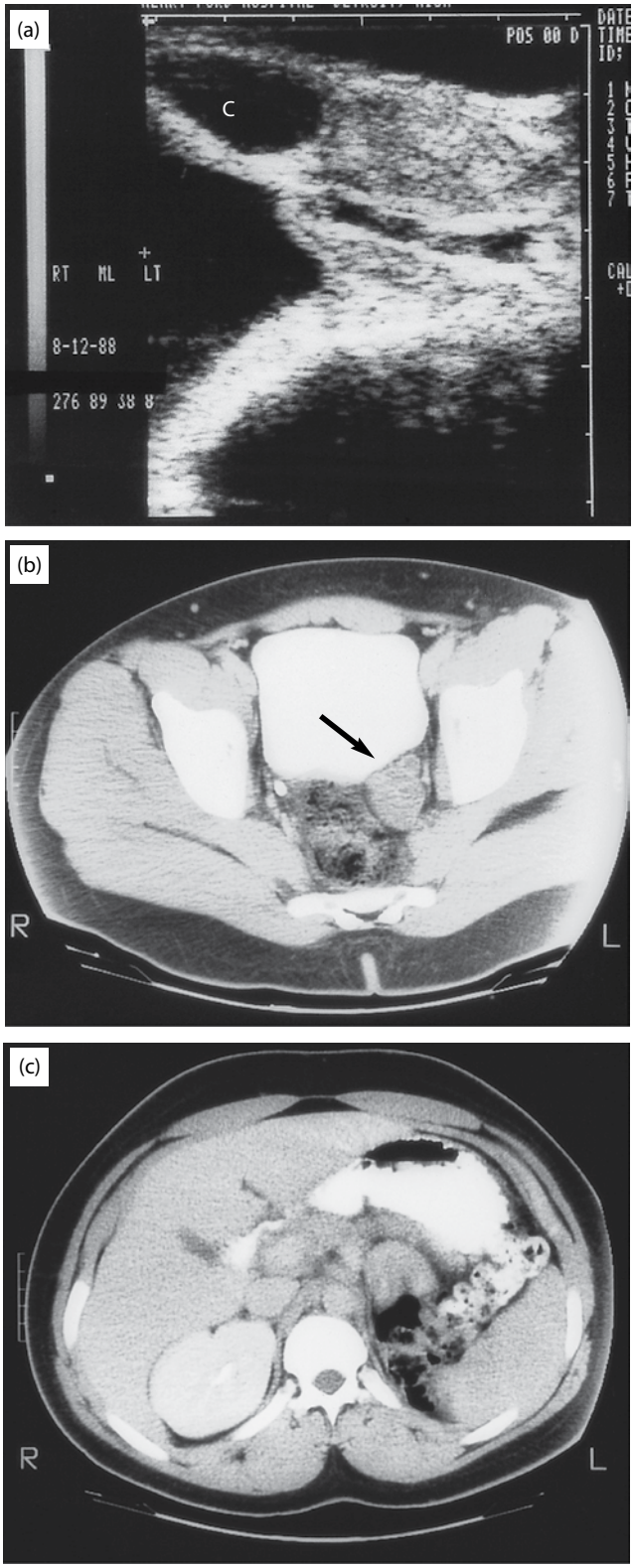

FIGURE 75.22 Seminal vesical cyst in an adolescent presenting with voiding symptoms and urinary tract infection: (a) sonogram showing a cystic structure posterior to the bladder in the left sagittal view (C); (b) computed tomographic (CT) scan confirming a fluid-filled structure (arrow) in the region of the left seminal vesicle; (c) absence of the left kidney on CT scan.

MULTIMEDIA FILES AVAILABLE ONLINE (WWW.CRCPRESS.COM/CW/DOCIMO)

VIDEO 75.1 Laparoscopic ligation for correction of varicocele.

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CHAPTER 76

Penile Replacement Surgery

Piet Hoebeke and Stan Monstrey

INTRODUCTION

The biological male without a penis or with a very insufficient penis remains a major challenge to the reconstructive surgeon. Next to congenital conditions in which the penile development failed, traumatic events, medically necessary penile amputations, and failed reconstructions of congenital anomalies are the main reason for penile insufficiency.

Severe penile insufficiency and absence of a penis are devastating conditions for men with a significant psychological and physical impact, and thus are a challenging lesion to treat.

Possible treatment options are gender reassignment, tailoring of the penile stump, penile replantation, phallic reconstruction (phalloplasty), and most recently, penile transplantation.

In the past, sex reassignment to the female gender has been offered, based on the principles applied to newborns with disorders of sex development (DSDs) and ambiguous genitalia. There is no evidence to show that the outcome of this policy is satisfactory. Indeed, long-term evaluation of a few patients shows contradictory results, which have triggered great controversy of this therapy.[92]

Today, sex reassignment is no longer considered a treatment of choice.

Tailoring of the penile stump by means of penile degloving, division of the suspensory ligament and rotational skin flaps, or skin grafts combined with buccal mucosa grafts for glans reconstruction has been reported. However, this can only be applied in cases of moderate penile injuries with still a reasonable penile stump.

Penile replantation can be attempted in the acute phase of traumatic amputation of the penis. The survival of the replanted penis depends on the viability of the amputated segment and the condition of the residual penile stump. Replantation must take place within 24 hours. Current replantation techniques rely on microsurgical approximation of the dorsal structures and cavernosal arteries with uniformly good results. In traumatic amputation, salvage of the amputated segment with replantation is the primary treatment option. The outcome of erectile function after replantation is not very clear.

Recently, one case report has been published on penile transplantation.[93] It is feasible due to microsurgical techniques with anastomosis of neurovascular structures, corporal bodies, and urethra, and due to our knowledge in immunosuppressive medication from other transplant surgery. Unfortunately, the transplanted penis was cut off 14 days postoperatively because of psychological problems of both the patient and his partner. This technique is still experimental and is not a current treatment option. Future options like tissue engineering are at present not science, but rather science fiction.

Nowadays, reconstructive surgery for severe penile insufficiency is performed within the context of a genitourinary reconstructive team, which includes urologists and plastic surgeons. The essence of a reconstructive team is reflected in this chapter, which mainly is the collaborative work of both these specialties. Plastic surgery techniques and traditions continue to play an important role in the reconstructive armamentarium of all who aim to repair genital defects. As the urethra is part of the genitals, the role of the urologist is essential in this reconstruction, as it is for erectile function.

In this chapter, we focus on penile replacement surgery for congenital and traumatic conditions with severe penile insufficiency and provide an overview of state-of-the-art approaches for this condition.

INDICATIONS FOR PENILE REPLACEMENT SURGERY

Congenital Genital Defects

Aphallia

Aphallia is an extremely rare condition in which a normally developed 46 XY male presents without a penis at birth. The scrotum is normally developed and the testes are also normal. The urethra ends in the perineum or in the anterior wall of the rectum (Figure 76.1).

Disorders of Sex Development

After standardization of the terminology, intersex conditions are nowadays defined as DSDs.[11] The conditions in which penile replacement could be a possible option include 46 XY DSD, chromosomal DSD, and some rare congenital anomalies. Where in the past an underdeveloped phallus could be an indication for female gender assignment, in modern times, with the actual state of penile replacement surgery, this assignment approach is no longer justified.

1. *46 XY DSD*: Undervirilization in males. Testosterone synthesis defects and partial androgen receptor insensitivity are among the causes. Patients in this group present genital ambiguity with varying degrees of

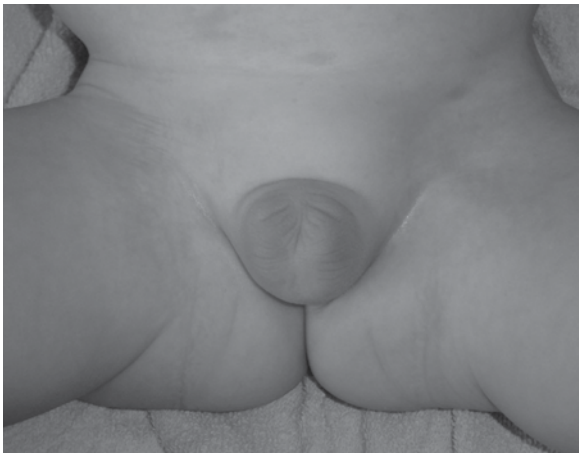

FIGURE 76.1 Aphallia. (Courtesy of Dr. R. De Castro.)

hypospadias, penoscrotal transposition, and cryptorchidism. Surgical treatment early in life consists of hypospadias repair, correction of penoscrotal transposition, and orchidopexy. In rare cases, the penis is so underdeveloped that penile replacement surgery can be an option.

2. *46 XY/46 XX DSD*: Consists of varying degrees of genital ambiguity and the presence of both male and female or dysgenetic gonads. Reconstruction is done after gender assignment, which is not always clear. Multidisciplinary teams with expertise in these pathologies are needed to guide the diagnosis and treatment in these children.
3. *Genital conditions*: This DSD classification includes conditions like penile agenesis, extreme penoscrotal transposition with rudimentary penis (Figure 76.2), cloacal exstrophy, idiopathic micropenis, and other genital malformations with normal chromosomes and gonads. All these conditions will eventually require genital reconstruction, although due to their low prevalence, these should be treated in centers of excellence by a multidisciplinary team with a lot of expertise in this field.

FIGURE 76.2 Complete penoscrotal transposition with rudimentary penis.

Traumatic and Iatrogenic Genital Defects

Penile Insufficiency after Failed Reconstruction for Exstrophy, Severe Hypospadias, and Cloacal Exstrophy

The main goal of initial closure for exstrophy is to reconstruct a functional genitourinary system. This is carried out by direct closure of the bladder and reconstitution of the pelvic ring. Different techniques have been described for penile reconstruction,[6,8] and although the results of the urethral closure have drastically improved, the ideal surgical approach is still controversial: neonatal versus delayed closure and one-stage versus multistage repair. Phallic length mainly depends on antenatal development, and the majority of these patients end up with a small and underdeveloped penis, despite the best efforts of their treating surgeons. As they pass through their postadolescent period, many of these young men will benefit from further lengthening procedures or even complete penile reconstruction. In some patients, correction of unaesthetic scars and further release of insufficiently released corpora can help to gain length (Figure 76.3).

In some boys, there is not enough skin to cover the penis after lengthening. For these cases, the thick split-thickness skin graft is the mainstay of reconstruction. The graft should be pliable, placed onto a flat bed, and secured with a tie-over bolus pressure dressing to reduce the risk of hematoma or seroma formation. Successful skin graft "take" is directly related to a well-vascularized wound bed, meticulous hemostasis, infection-free environment, and adequate immobilization.

The donor site should be close to the genitalia, large enough to produce a sheet skin graft, and well hidden. Ideally, the skin graft should be at least 0.018–0.02 inch in thickness and large enough to cover the whole breadth of the penile shaft or scrotum. The skin graft should be sutured circumferentially around the penile shaft with a ventral suture line. The graft is then fixed to the surrounding skin, the underlying Buck's fascia, and the tunica with dissolving sutures. Fixation with tissue sealant has been reported to improve skin graft fixation and skin graft take in this difficult area.[16]

Widely meshed split-thickness skin grafts should never be used on the penile shaft. However, with the so-called "reversed mesh graft" (nonexpanded or 1:1 meshed skin grafts), only puncture-type perforations are made with a V1 carrier (Humeca Ltd., Enschede, the Netherlands) (Figure 76.4), which allows for a better fluid evacuation, and thus a better skin graft take, while still avoiding poor scarring and an unaesthetic mesh pattern in the long term. These nonexpanded meshed split-thickness grafts have also become a mainstay of complicated, staged urethral

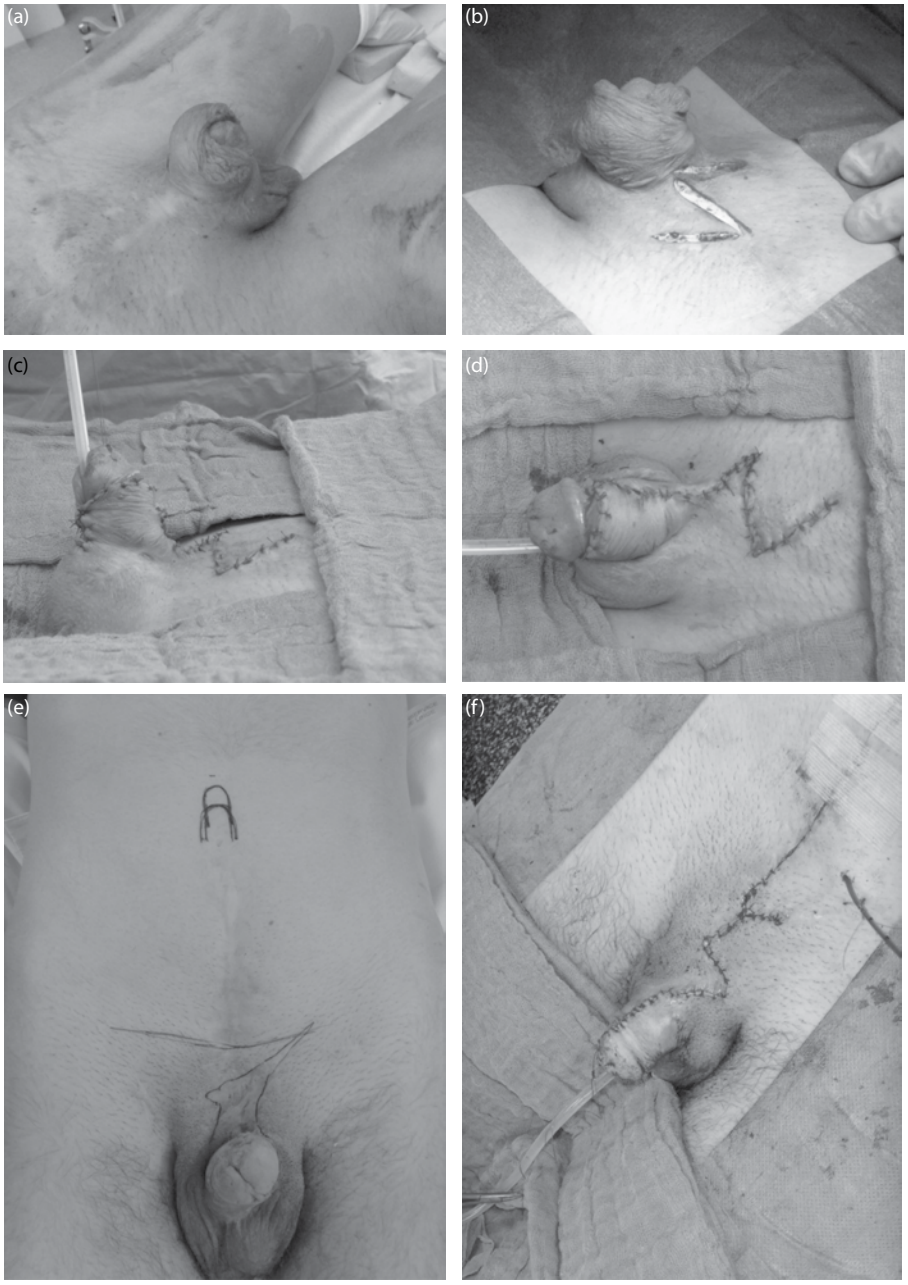

FIGURE 76.3 Examples of Z-plasty on the dorsal aspect of the penis extending into the prepubic area to obtain maximal lengthening (a–f).

reconstruction[17,18] McAninch[19] has described the use of (not too widely) meshed split-thickness skin grafts for scrotal reconstruction. Meshed grafts in this location may produce "good aesthetic results," but they will never measure up to the functional capacity of sheet or 1:1 perforated grafts.

The use of this reversed mesh graft is shown in two cases in Figure 76.5.

Unfortunately, in some boys there just is not enough tissue due to underdevelopment or partial or complete loss of penile tissue after primary closure. These patients might be good candidates to undergo a phallic construction or further penile reconstruction with the use of microsurgical tissue transplantation techniques or local pedicled perforator flaps (Figure 76.6).

Most of these patients have some form of continent urinary diversion, and therefore a nonfunctional urethra. Although the ejaculatory ducts are mostly intact, they are often abnormally positioned as a prepubic fistula. These anatomic facts create unpredictable sperm production. For these reasons, the urethral reconstruction may be a moot point in this group of patients, thus making a phalloplasty in these "boys without a penis" much easier than a penile reconstruction in a patient who wants to void through his new penis. The different options and peculiarities for a phalloplasty in an exstrophy patient will be addressed further in this chapter.

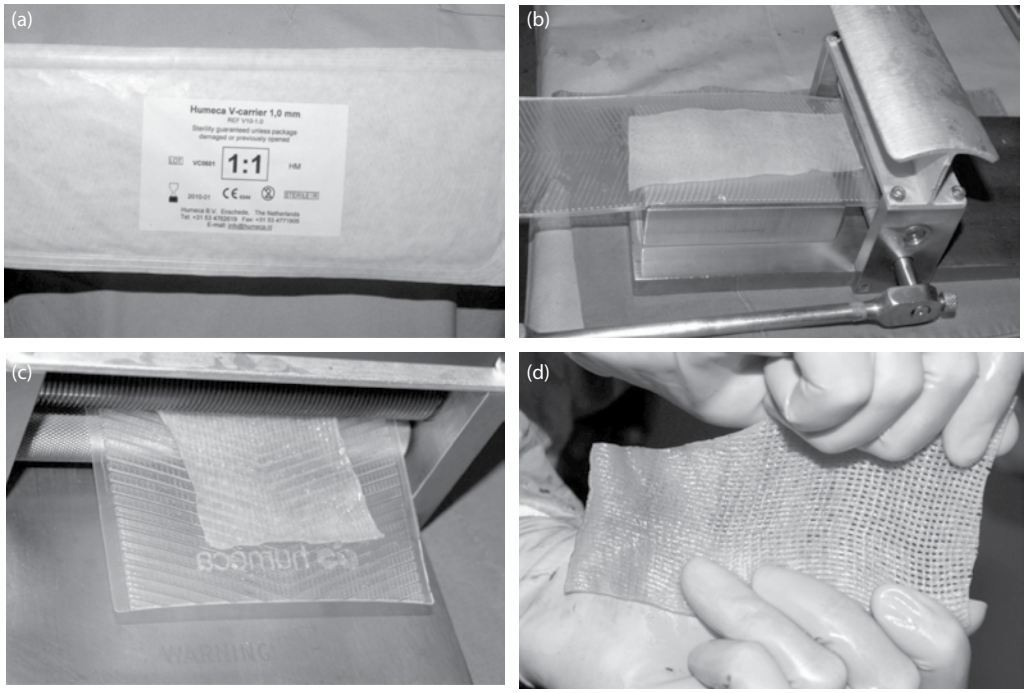

FIGURE 76.4 Reversed mesh graft (a–d).

Penile Trauma

Posttraumatic Genital Reconstruction

Posttraumatic genital repair is an uncommon but special chapter in surgical reconstruction. A reconstructive algorithm based on the etiology, an assessment of the extent of injury, and an anatomic inventory includes several goals and observations. First, the anatomically protected position of the genitalia implies that patients who have genital injuries often have large concomitant injuries as well, and are often

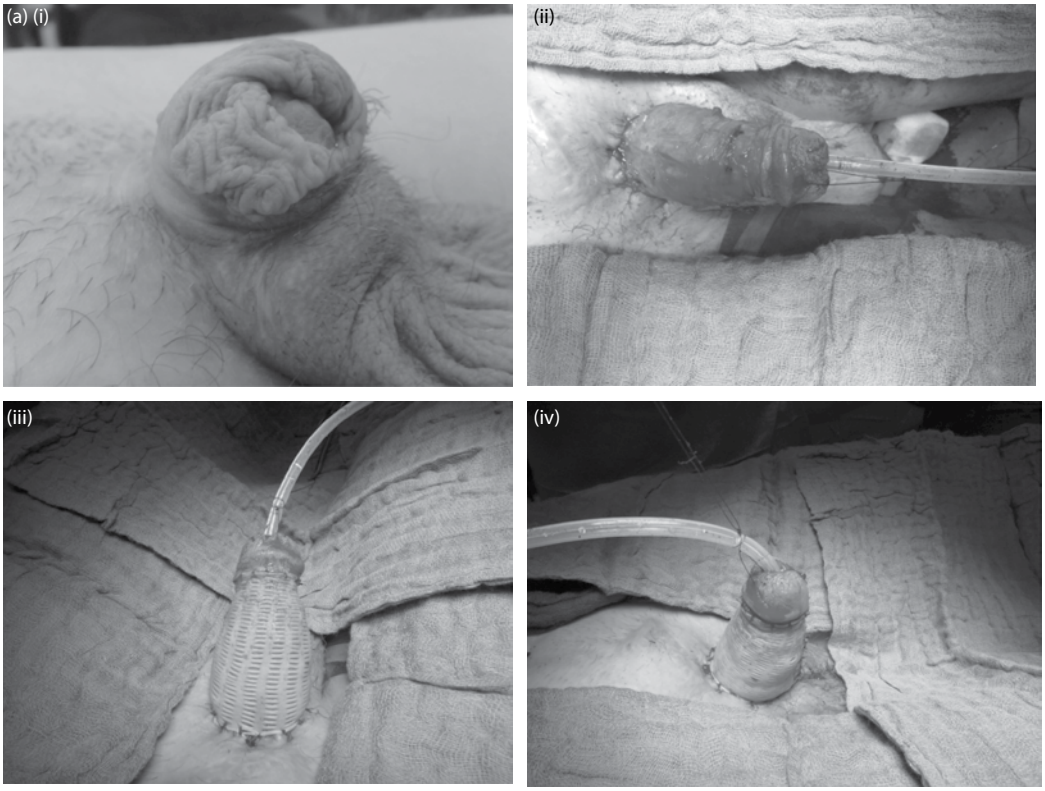

FIGURE 76.5 (a)(i)–(iv) Reversed mesh graft in complex exstrophy. (*Continued*)

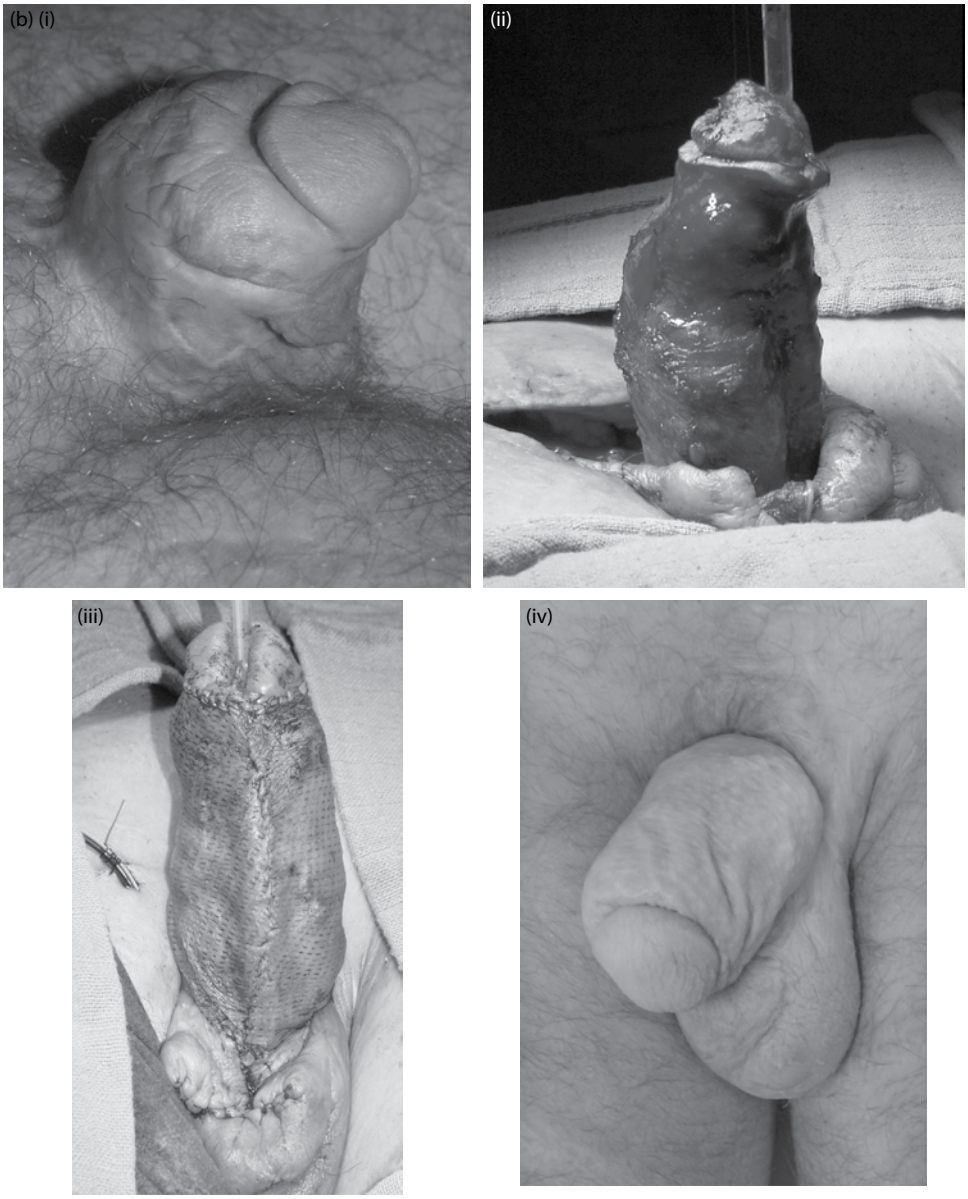

FIGURE 76.5 (Continued) (b)(i)–(iv) Reversed mesh graft in case of complex hypospadias.

critically ill. Resuscitation and life support of the patient take precedence over any reconstruction. However, genital reconstruction is of prime relevance, and only hand, eyelid, and lip reconstruction are considered more important in the reconstructive hierarchy. Second, aesthetics are foremost in genital reconstruction. Although it is not often articulated, the appearance of the genitalia is important to the self-esteem of a patient who is recovering from trauma. What is frivolous to one person may be a lifelong obsession to another, and genital aesthetics are as valued as other cosmetic areas, such as the face, nose, and breasts. Third, the genitalia appear to be a "privileged site," such that the usual postreconstructive sequelae of scarring and contracture are often spared in genital reconstruction. This may be due to the fact that the average adult man has five to eight nocturnal erections every night, thereby inherently stretching scars or skin grafts on the penile shaft. This stretching may combat and overcome the tendency of myofibroblasts to contract a skin graft or scar.

Buccal mucosa grafts are often used in urethral reconstruction. They can also be useful in glans reconstruction. After partial penectomy (traumatically or for cancer treatment), the residual corpora sometimes are still long enough to allow for sexual intercourse. However, the penis is completely covered with skin, which leads to an unnatural look. For these patients, the corpora can be released by transsection of the suspensory ligament and the tip of the corpora can be covered by buccal mucosa-free grafts. They create a mucosa-covered glans-like-looking tip of the penis (Figure 76.7a–c).

Genital Replantation

Microsurgical techniques and free tissue transplantation have become the state-of-the-art treatment for many reconstructive problems. The first uses of the microscope in genital reconstruction for penile reattachment

FIGURE 76.6 Examples of patients who are candidates for undergoing phalloplasty (a–d).

after amputation were reported independently by Cohen et al.[43] and Tamai et al.[44] in 1977. However, the first account of successful reattachment long predated the introduction of microsurgical techniques. In 1929, Ehrich[45] first reported a successful penile attachment by opposing and anatomizing the lacerated corporal bodies and repairing the overlying tunica only. This technique was occasionally successful but usually associated with loss of the overlying skin, glans, sensation, and erectile and voiding function.[46]

Penile replantation often mimics the algorithms of other amputated extremities that are candidates for

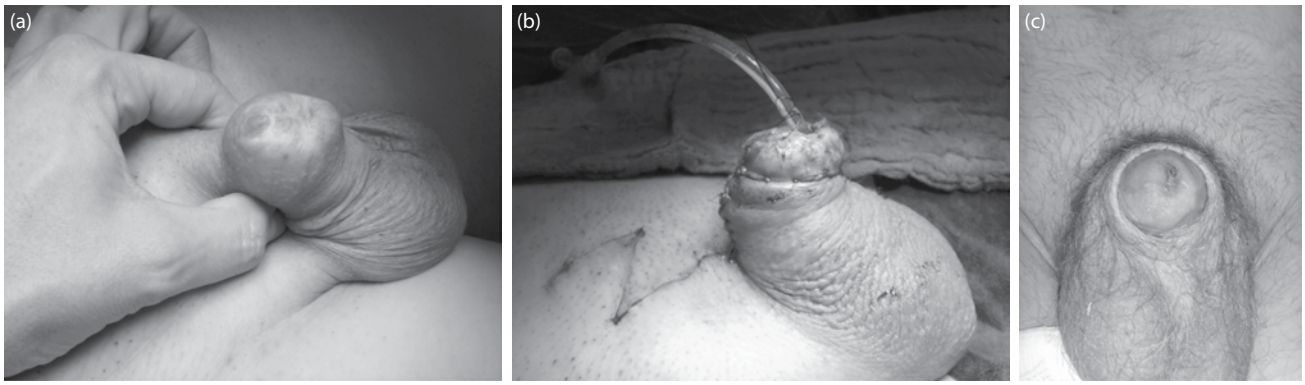

FIGURE 76.7 (a) Penis after partial penectomy for spinocellular epithelioma, showing residual corpora that, after release, could be sufficient for sexual intercourse. (b) After penile elongation with release of the suspensory ligament and coverage of the distal part of the penis with buccal mucosa. (c) Result of glans reconstruction using buccal mucosa.

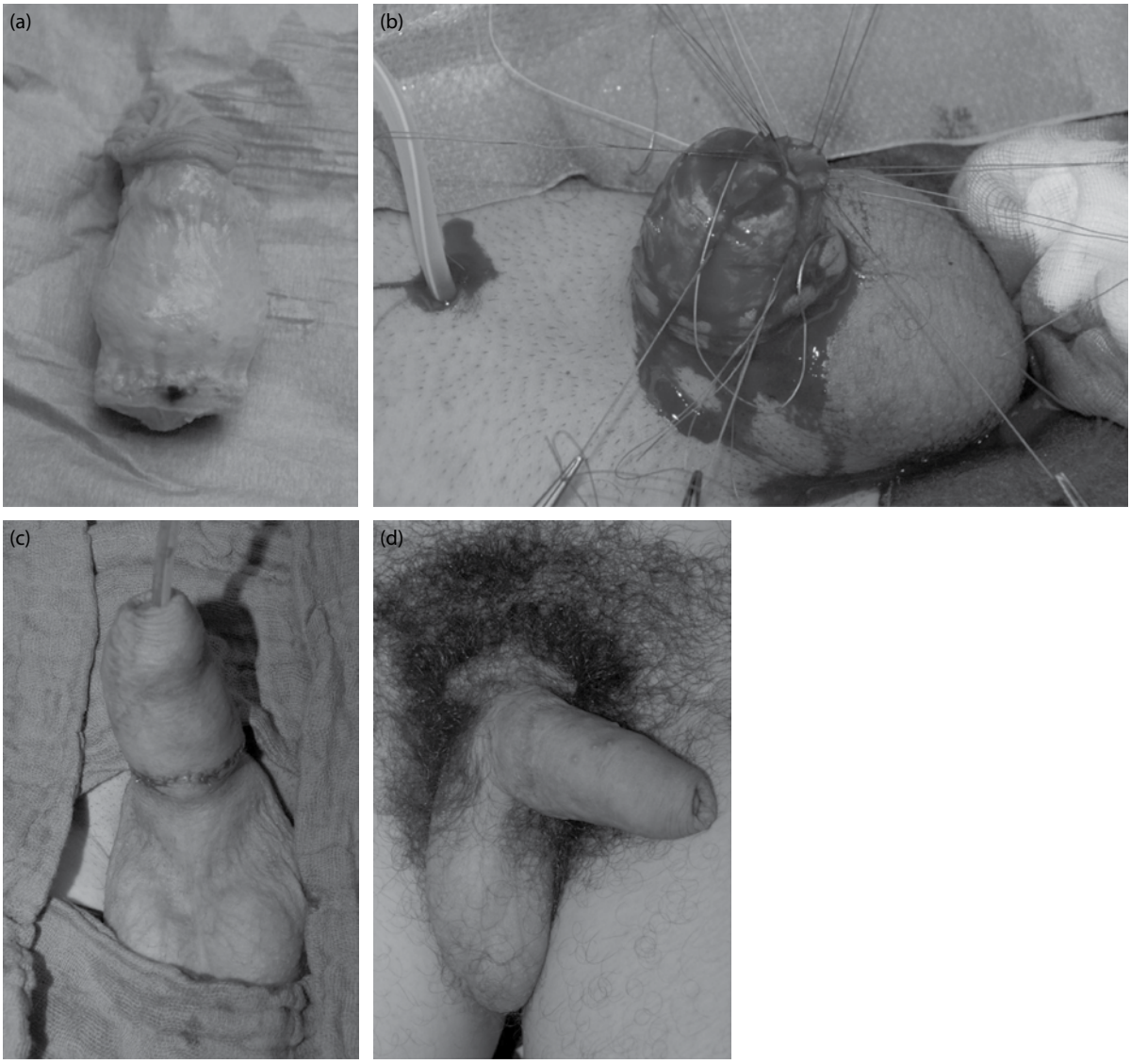

FIGURE 76.8 (a) Self-inflicted penile amputation. (Courtesy of Dr. Nathalie Roche.) (b) Preparation of microsurgical anastomoses. (Courtesy of Dr. Nathalie Roche.) (c) Immediate postoperative result. (d) Late postoperative result.

reattachment. The penis is initially wrapped in saline-soaked gauze and placed into a plastic bag, which in turn is placed in a bag or cooler of ice with water (the so-called "bag-in-a-bag" technique). Because genital amputations are often self-inflicted, it is important to involve the psychiatrist even before restorative surgery. After the induction of anesthesia, the proximal and distal ends of the amputated penis are examined microscopically. Minimal debridement is followed by mechanical stabilization of the urethra and reapproximation of the tunica albuginea of the corpora cavernosa.

Revascularization is completed by use of microsurgical magnification, instrumentation, and 9-0 and 10-0 nylon sutures to reanastomose the deep dorsal arteries, the deep dorsal vein, and the superficial dorsal vein. Multiple nerve coaptations are meticulously completed with 10-0 and 11-0 nylon sutures. The dartos fascia and skin are then loosely approximated to complete the reattachment. A suprapubic tube is inserted to divert the urinary flow for 2–3 weeks, and the patient is prescribed bed rest in a warm room.

The ideal candidate for genital replantation is a patient with a clean, sharp cut in which the amputated part has been cooled (Figure 76.8a–d).

RECONSTRUCTION OF MALE GENITALIA IN SEVERE PENILE INSUFFICIENCY

There is still a lot of controversy regarding whether to perform a phalloplasty in children. Penile construction in children is similar to that in adults with one added requirement—growth through puberty to adulthood. Because the phallus is constructed of somatic tissues (showing linear

growth) but replaces a penis that is formed by genital tissues (demonstrating a more exponential growth), the growth rates are temporally and quantitatively different during puberty.[14] Care must be taken to accurately predict the anticipated growth rate and to design a phallic model that is larger and longer than the normal genital size for that age group.[15]

Furthermore, the body proportions between prepubertal boys and postpubertal boys are different. The extremities are proportionally bigger in infants than the rest of the body. Using flaps from extremities will result in a disproportionate penis. An alternative proposed by Roberto De Castro consists of the creation of a phallus based on an abdominal flap.[95] Despite the surgical feasibility of this technique, the advantage should be weighed against the possible disadvantage. The advantage is the fact that the patient, as a child, will identify more easily as being a boy and should experience less stress, but this does not outweigh the disadvantage that the abdominal phallus will remain small after puberty, while the lower abdominal scar can interfere with the outcome of future state-of-the-art phalloplasty.

Another issue that we are just now beginning to address is the "correct" age at which to proceed with the insertion of penile prostheses. Once these boys have reached 18 years and the age for majority, they must be physically and psychologically prepared to manage a phallus that has previously been erectionless.

There is another nagging problem with operating on children—the lack of informed consent. Although the child's best interest and surgery's best intentions are usually served by early reconstruction, there are no long-term studies that have evaluated the results of this surgery over a lifetime or even a generation.

Finally, it comes as no surprise that the large majority of these genitally compromised boys require prolonged psychological therapy to deal with genital loss, surgical trauma, inadequacy, and scarring. These psychological issues are often closely commingled with the need for secondary surgery to complete reconstruction.

Complete Phallic Reconstruction

The term *phalloplasty* was first used in 1858 by Sprengler to indicate the reconstruction of the integument after decollement (separation of the superficial tissue layers) of the penis.[56] Bogoras, the first to report on the reconstruction of the entire penis, labeled his procedure "penis plastica totalis."[57] He was also the first to use a single abdominal tube, a technique later applied by others. Subsequently, *phalloplasty* was used to describe penile reconstruction.

Following World War II, some leading plastic surgeons showed an interest in the penile reconstructive procedure. In 1948, McIndoe[58] improved the abdominal tubed flap by constructing a neourethra while raising the pedicle tube employing an inlay skin graft. Maltz[59] and Gillies[60] popularized the technique when they added a costal cartilage graft as a rigidity prosthesis. Gillies was the first to report the use of this technique in a transsexual patient. The Stanford team[55,61] refined the procedure, tubing an infraumbilical abdominal flap outside in, in order to create a skin-lined tunnel as a future urethral conduit. This method reduced the number of stages previously necessary for phalloplasty.

Snyder described a phalloplasty technique incorporating a preconstructed superficial skin-lined conduit for intersex patients employing a single pedicled infraumbilical skin flap.[62,63] Hester et al. performed a penile reconstruction in one stage using a vertical, superficial inferior epigastric artery flap with a subcutaneous pedicle, in a male born with ambiguous genitalia.[64] However, after McGregor and Jackson introduced the groin flap in 1972,[25] Hoopes[65] commented that "the groin flap may prove the method of choice for phallus reconstruction." Orticochea[66] used a gracilis myocutaneous flap in a five-stage phalloplasty procedure, and claimed it produced cosmetically and functionally superior results. The Norfolk team also used a unilateral gracilis myocutaneous flap for phalloplasty.[40] Sometimes, a combination of flaps was used. Exner[67] implanted a ridigity prosthesis in a rectus abdominis muscular flap and used bilateral groin flaps to cover the neophallus.

Once microsurgery established a foothold in genital construction, plastic surgeons began to explore and map out the genital neurovascular supply and to consider expanding the applications of microsurgery to elective reconstruction of the genitalia. Chang and Hwang[68] described an ingenious adaptation of the tube-in-tube concept into a free tissue transfer with the radial forearm flap originally described by Song et al.[69]

Since the early reports, a wide variety of other free flaps have also been described for phalloplasty, including the dorsalis pedis flap,[70] the deltoid flap,[71] the lateral arm flap,[72] the fibular flap,[73] the tensor fasciae latae flap,[41] the anterolateral thigh (ALT),[74] and the deep inferior epigastric artery perforator (DIEAP) flap.[75] The fact that so many techniques for penile reconstruction exist is evidence that none are considered ideal. Still, most of these articles are only case reports or small series, and even nowadays the "old" Chinese flap or radial forearm flap is by far (>90%) the most frequently used free flap in the literature,[75] and is therefore often considered the gold standard for penile reconstruction. Monstrey et al. recently published the only large (287 patients) and well-documented (long) term follow-up study on the use of the radial forearm phalloplasty.[75] They describe the technique they used in almost 300 consecutive cases and evaluated to what degree this supposed gold standard technique has been able to meet the ideal goals in phallic reconstruction. This group also reported the first large series of penile replacement surgery for severe penile insufficiency.[96] In their first report, they report on seven radial forearm flaps and four ALT flaps. Both techniques are described with their advantages and disadvantages.

Radial Forearm Flap: Technique and Long-Term Results

The creation of a phallus with a tube-in-a-tube technique is performed with the flap still attached to the forearm by its vascular pedicle. A small skin flap and a skin graft are used to create a corona and simulate the glans of the penis (Figure 76.9a–f).

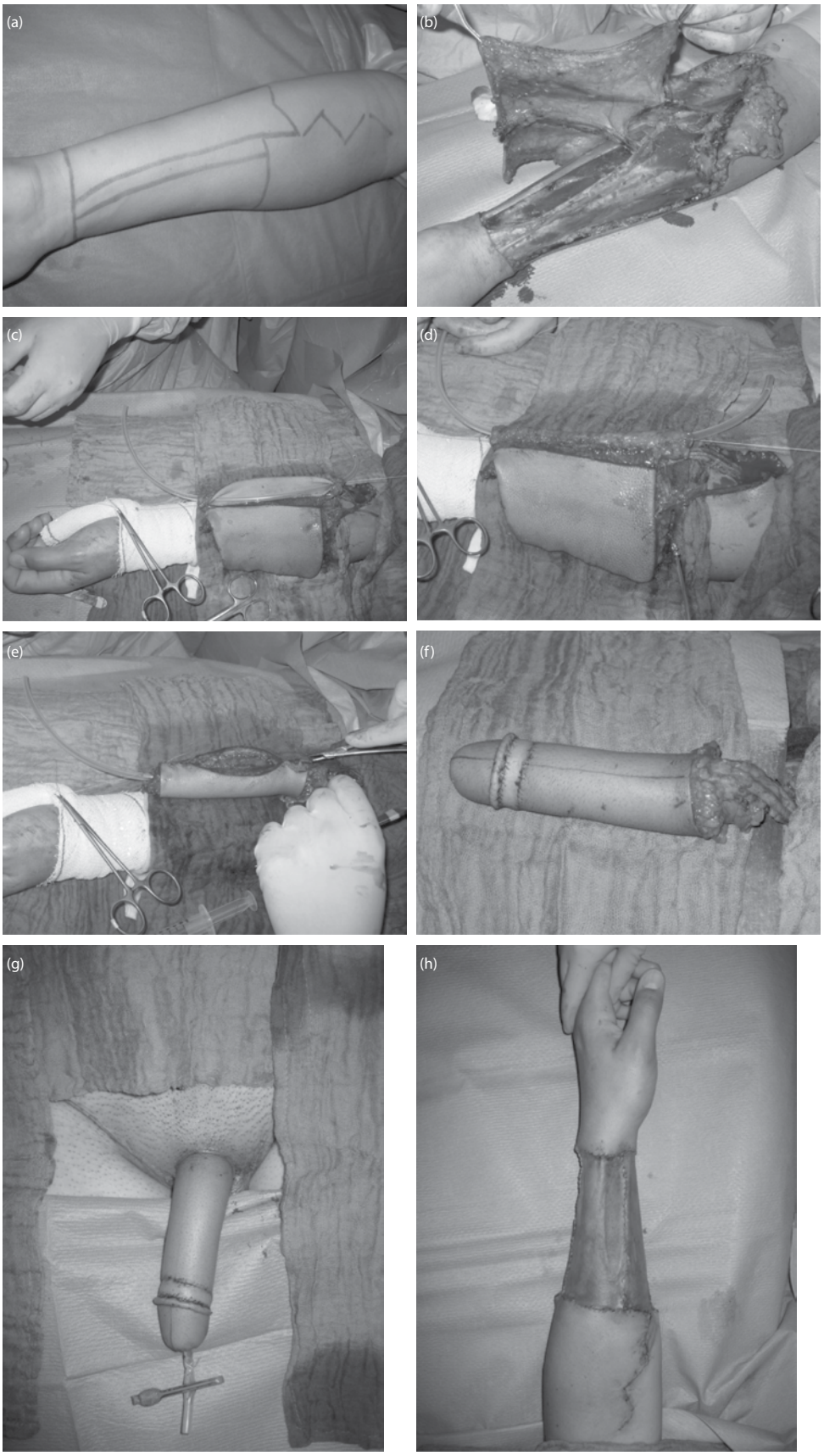

FIGURE 76.9 Standard radial forearm technique: (a) Design and (b) dissection of the flap. (c and d) Tubing (inner tube) of the urethra. (e) Outer tube of the penis itself. (f) Creation of the glans of the penis (with penis still attached to the forearm, just prior to transfer to the pubic area. Immediate postoperative result of (g) the penis and (h) the donor site on the arm.

When a urethral reconstruction is needed, the urologist prepares the native urethra for connection. After former reconstructions of the urethra, most scar tissue is removed and healthy mucosa is exposed to anastomose to the flap urethra. The free flap can be transferred to the pubic area after the urethral anastomosis (Figure 76.9g and h): the radial artery is microsurgically connected to the common femoral urethra in an end-to-side fashion, and the venous anastomosis is performed between the cephalic vein and the greater saphenous vein. One forearm nerve is connected to the ilioinguinal nerve for protective sensation, and the other nerve of the arm is anastomosed to one of the dorsal penile nerves for erogenous sensation.

The average hospital stay for the phalloplasty procedure is 2½ weeks.

Tattooing of the glans can be performed after a 2- to 3-month period, before sensation returns to the penis.

Phallic construction had become predictable enough to refine its aesthetic goals, which include the use of a technique that can be replicated with minimal complications. In this respect, the radial forearm flap has several advantages: the flap is thin and pliable, allowing the construction of a normal-sized, tube-within-a-tube penis; the flap is easy to dissect and is predictably well vascularized, making it safe to perform an (aesthetic) glans-plasty at the distal end of the flap. The final cosmetic outcome of a radial forearm phalloplasty is a subjective determination, but the ability of most patients to shower with other men or to go to the sauna is the usual cosmetic barometer (Figure 76.10).

The potential aesthetic drawbacks of the radial forearm flap are the need for a rigidity prosthesis and possibly some volume loss over time.

Of the various flaps used for penile reconstruction, the radial forearm flap has the greatest sensivity.[78] Monstrey et al. always connect one antebrachial nerve to the ilioinguinal nerve for protective sensation, and the other forearm nerve with one genital nerve (clitoral nerve in transsexual patients and dorsal penile nerve in males).

After 1 year, all patients had regained tactile sensitivity in their penis, which is an absolute requirement for safe insertion of an erection prosthesis.[78]

In a long-term follow-up study on postoperative sexual and physical health, more than 80% of the patients reported improvement in sexual satisfaction and greater ease in reaching orgasm (100% in practicing postoperative female-to-male [FTM] transsexuals).[79]

For biological males as well as FTM transsexuals undergoing a phalloplasty, the ability to void while standing is a high priority.[80] Unfortunately, the reported incidences of urological complications, such as urethrocutaneous fistulas, stenoses, strictures, and hairy urethras, are extremely high in all series of phalloplasties, even up to 80%.[35] For this reason, certain (well-intentioned) surgeons have stopped reconstructing a complete neourethra.[74,82]

In their series of radial forearm phalloplasties, Monstrey et al.[75] still reported a urological complication rate of 41% (119/287), but the majority of these early fistulas closed spontaneously, and ultimately *all* patients were able to void through the newly reconstructed penis.[83]

The major drawback of the radial forearm flap has always been the unattractive donor site scar on the forearm (Figure 76.11a and b). Selvaggi et al. conducted a long-term follow-up study[84] of 125 radial forearm phalloplasties to assess the degree of functional loss and aesthetic impairment after harvesting such a large forearm flap. An increased donor site morbidity was expected, but the early and late complications did not differ from the rates reported in the literature for the smaller flaps, as used in head and neck reconstruction.[84] No major or long-term problems (such as functional limitation, nerve injury, chronic pain or edema, or cold intolerance) were identified. Finally, with regard to the aesthetic outcome of the donor site, they found that the patients were very accepting of the donor site scar, viewing it as a worthwhile trade-off for the creation of a phallus.[84] Suprafascial flap dissection, full-thickness skin grafts, and the use of dermal substitutes may contribute to a better forearm scar.

Anterolateral Thigh Flap

The development of perforator flaps has given rise to some new reconstructive options in patients with severe (congenital) penile insufficiency. Perforator flaps have the advantage of reducing the donor site morbidity, increasing the range of motion, and combining different tissue flaps on one single pedicle. Although, overall, the free vascularized radial forearm flap, the pedicled ALT flap is considered the gold standard phalloplasty alternative specifically in patients with congenital penile insufficiency. This flap is a skin flap based on a perforator from the descending branch of the lateral circumflex femoral artery, which is a branch from the femoral artery (Figure 76.12).

The potential advantages of the ALT flap are

- A pedicled flap reconstruction (the flap has a sufficiently long pedicle) avoids the technically more complex microscopic procedure and might also shorten the operation time.
- A visible donor site scar on the forearm, often considered the signature of FTM transsexualism, is avoided and the donor site on the leg can more easily be concealed.
- Previous reconstructive surgeries at the pelvis, groin area, and lower abdomen (e.g., in case of bladder exstrophy) might have altered the local anatomy and vasculature, making a microsurgical anastomosis more difficult.
- The subcutaneous fat layer is much thinner than in a (biologically female) trans man, facilitating the (urethral) tube-within-a-(penile)-tube reconstruction of the penis; moreover, many exstrophy patients empty their bladder by catheterization through a continent diversion (e.g., appendicovesicostomy) and do not even require a urethral reconstruction in their phalloplasty. An ejaculatory opening can be left at the ventral aspect just above the scrotum.

It is very important to preserve and incorporate any useful glandular, penile, and cavernosal tissue at the base

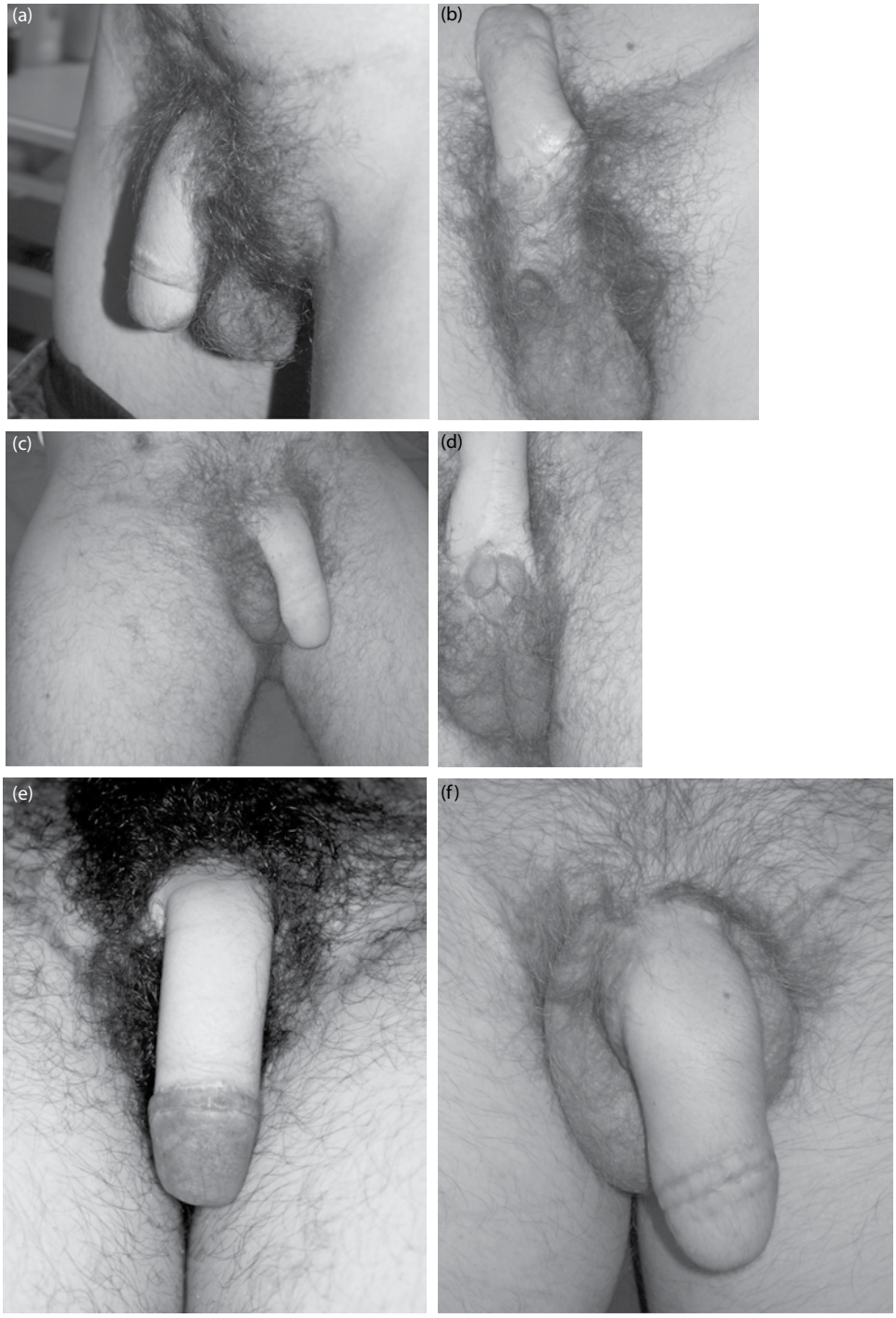

FIGURE 76.10 Late postoperative results of radial forearm phalloplasties.

of the newly reconstructed phallus in order to facilitate sexual stimulation and pleasure (Figure 76.11c). If available, a dorsal penile nerve is identified and connected with a cutaneous nerve of the flap; if not available, the lateral femoral cutaneous nerve is connected to the ilioinguinal nerve.

Usually, it is recommended to perform a three-dimensional angio CT scan preoperatively to provide detailed information on the perforator vessels and the subcutaneous tissue layer.

Unfortunately, similar to the radial forearm flap, the ALT flap also has a rather high urological complication rate, with frequent strictures and/or fistula formation. Secondary procedures might be needed to treat these complications, and especially the treatment of urethral strictures is challenging and difficult.

Especially in exstrophy repair where the closure of the pelvic ring has been unsuccessful and the distance to the femoral vessels is large, this flap is a good option. Some examples are show in Figure 76.13.

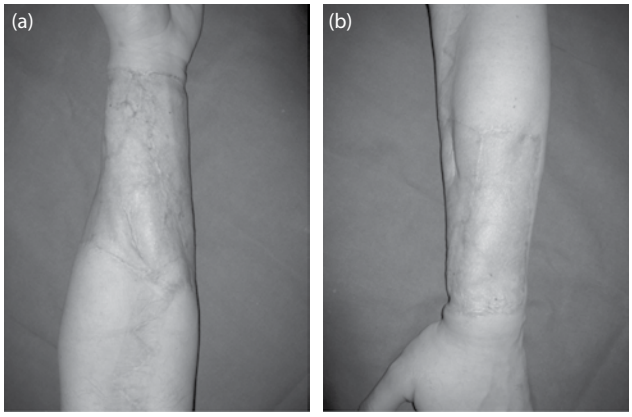

FIGURE 76.11 (a and b) Late result of the donor site at the forearm.

Erection Prosthesis

In phalloplasty, the insertion of an erection prosthesis is required in order to engage in sexual intercourse. In the past, attempts have been made to use bone or cartilage, but no good long-term results are described. The rigid and semirigid prostheses seem to have a high perforation rate and therefore were initially not used in our patients. Hoebeke et al., in the largest series to date on erection prostheses after penile reconstruction, only used the hydraulic systems available for impotent men. A recent long-term follow-up study showed an explantation rate of 44% in 130 patients, mainly due to malpositioning, technical failure, or infection. Still, more than 80% of the patients were able to have normal sexual intercourse with penetration.[83] In another study, it was demonstrated that patients with an erection prosthesis were more able to attain their sexual expectations than those without a prosthesis (Figure 76.14a and b).[79]

A major concern regarding erectile prostheses is long-term follow-up. These devices were developed for impotent (older) men who have a shorter life expectancy and who are sexually less active than the mostly younger patients with penile insufficiency. More specifically, the hydraulic systems tend to be susceptible to leak after 5–10 years. Actually, some newer semirigid devices have become available that hopefully are more durable and will decrease the need for revision surgery.

GENERAL CONCLUSION

In this chapter, an overview of actual reconstructive techniques for severe penile insufficiency was given.

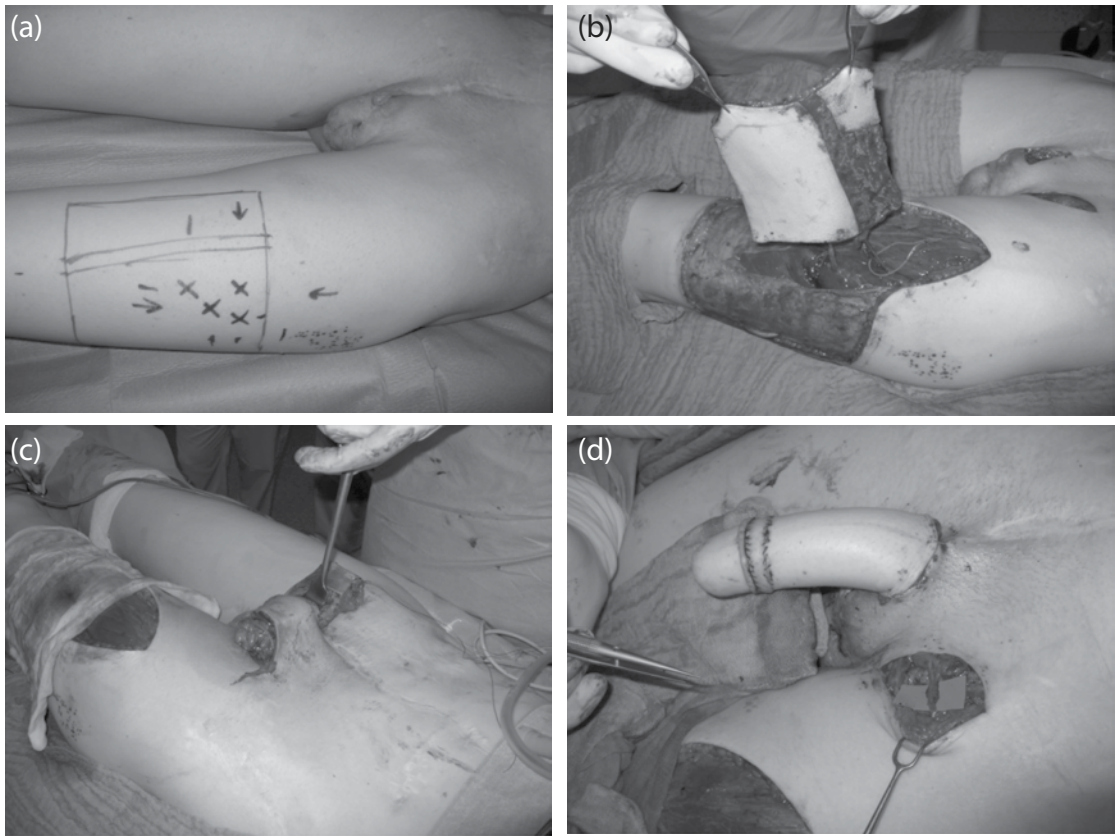

FIGURE 76.12 (a and b) The reconstruction of a penis with a pedicled ALT flap used as a tube-within-a-tube technique (only possible in thin boys without a penis and after defatting). No real urethra was reconstructed here since the patient had a urostomy. (a) Preoperative view. (b) After flap dissection. (c) The flap is tunneled underneath the rectus femoris muscle. (d) Suturing and nerve connection (ilioinguinal nerve to lateral femoral cutaneous nerve).

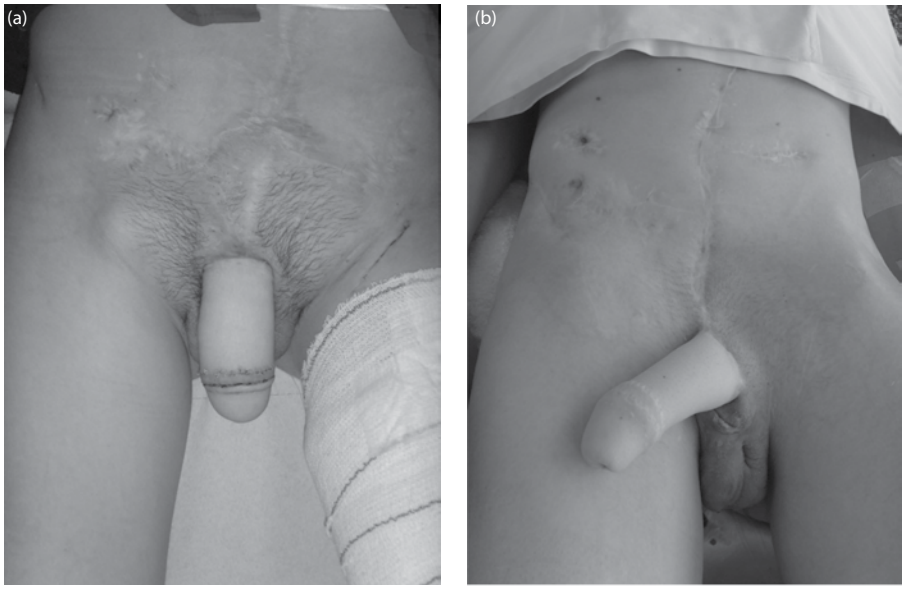

FIGURE 76.13 ALT flap phalloplasty in two boys with a history of cloacal exstrophy.

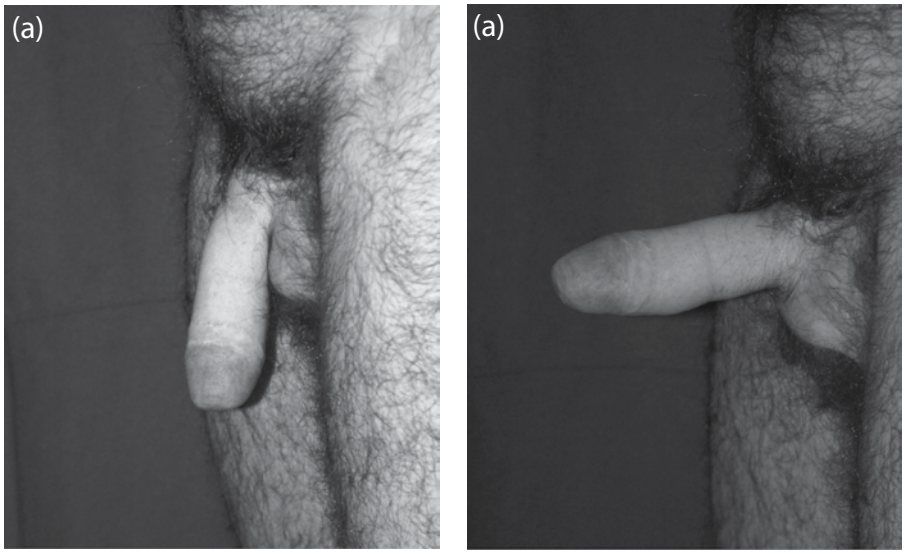

FIGURE 76.14 (a and b) After implantation of an erection prosthesis.

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CHAPTER 77

Hernia, Hydrocele, Testicular Torsion, and Varicocele

Hiep T. Nguyen and Guilherme Rossini

INTRODUCTION

Problems associated with the testis, such as hernia or hydrocele, testicular torsion, and varicocele, are common in infants and children. These conditions range in acuteness and severity, from being one of few pediatric urologic emergencies to a benign process that is likely to resolve and therefore warrant just observation. While their diagnosis can be difficult to make at times, problems associated with the testes mandate accurate and prompt recognition in order to prevent potential testicular damage or loss. Their management options are often diverse and controversial, requiring the clinician to be aware of these issues in counseling the patients or their parents. While these conditions can be correct surgically, they may have long-term consequences, such as testicular atrophy and infertility, requiring further follow-up care after surgical management.

HERNIA AND HYDROCELE

Definition and Incidence

An inguinal hernia is defined as a protrusion of organ or tissue through an abnormal opening in the lower abdominal wall. A direct inguinal hernia results from a weakness in the floor of the inguinal canal, allowing abdominal content and fluid to herniate through the external ring, medial to the epigastric vessels. In contrast, an indirect inguinal hernia results from a patent *processus vaginalis* (PV), allowing abdominal content and fluid to herniate through the internal ring. A direct inguinal hernia is uncommon in children, while an indirect one is more common in this age group. A hydrocele is defined as an accumulation of fluid around the testis. A communicating hydrocele results from a patent PV in which the opening through the internal ring is small, allowing fluid but not bowel to enter the scrotum. A noncommunicating hydrocele results from a patent PV in which the opening through the internal ring is closed, but the PV is not completely obliterated. Since there is no communication with the peritoneum, the fluid in the noncommunicating hydrocele originates from the mesothelial lining of tunica vaginalis as a result of inflammation of the testis or epididymitis. A communicating hydrocele is common in children, while a noncommunicating hydrocele is more common in adolescents.

Hernia and hydrocele occur in approximately 1%–3% of full-term infants, but are three times more common in premature infants.[1,2] With regards to hernia, the male-to-female ratio is 8 to 1. A hernia or hydrocele occurs more often on the right than the left (2:1) and is present bilaterally in 16% of the patients.[1] Ten percent of children with a hernia or hydrocele will have a positive family history. Approximately one-third of the children with a hernia or hydrocele will be diagnosed before 6 months of age. An increased incidence of hernia or hydrocele is seen in patients with cystic fibrosis (15%);[3] connective tissue disease, such as Ehlers–Danlos and Hunter–Hurler syndrome;[4,5] and congenital hip dislocation.[6] Children with a ventriculoperitoneal shunt or on peritoneal dialysis continuous ambulatory peritoneal dialysis (CAPD) are also at higher risk of developing a hernia or hydrocele.[7]

Etiology and Pathophysiology

In the male fetus, the testes develop from the cranial end of the mesonephros. The gubernaculum forms from a band of condescended mesenchyme, connecting to the lower pole of each testis. Around the eighth week of gestation, an outpouching of mesothelial cells from the coelomic cavity grows into the substance of gubernacular mesenchyme, forming the PV. The PV is composed of a lining of simple mesothelium, surrounded by a fibrous layer of variable thickness and fatty connective tissue containing blood vessels, nerve trunks, lymph nodes, and a variable amount of muscle.[8] The skeletal muscles of the PV are derived from the transverse abdominis muscle, and the smooth muscle component is derived from the dartos muscles. Occasionally, the lining of the PV undergoes proliferation due to chronic irritation. It may contain papillary structures or nodules. On histologic examination, fibrin deposition, extensive scarring, and psammoma bodies may be evident. In addition, mesothelial hyperplasia may be present with multinucleated cells, forming tubule-like structures within the fibrous tissue. These structures may appear to invade into the fibrous subserosa of the irritated PV. These features are often confused with those of rhabdomyosarcoma, mesothelioma, and metastatic carcinoma.[9]

By the 28th week of gestation, the testes begin to move from the posterior abdominal wall to the internal ring, as a result of growth of the fetal trunk and pelvis. The PV forms a channel through which the testes descend into the scrotum. It is believed that testicular descent is directed by the gubernaculums[10] and assisted by the PV, which allows transmission of the abdominal pressure to the fetal testes, causing their descent through the inguinal canal.[11] The passage through the inguinal canal takes approximately 3 days and appears to be regulated by the genitofemoral nerve and the release of the calcitonin gene-related peptide (CGRP).[12,13] The testes enter the scrotum between the 32nd and 38th week of gestation; in some patients, this process may be delayed up to the 40th week of gestation.

After the descent of the testes, the entrance to the inguinal canal, the internal ring, closes and the lumen of the PV is obliterated. Progressive fibrous obliteration of the PV occurs in a cephalad direction beginning above the epididymis.[14] Organ culture of the PV from human infants demonstrates the presence of a CGRP receptor on the mesechymal fibroblasts, but not the epithelial cells. Addition of CGRP induces fusion of the PV through its effects on the fibroblasts.[13] In the future, CGRP may be utilized in the clinical management of hernia or hydrocele in children.[15] In addition, it is observed that a patent of the PV is often seen in association with epididymal abnormalities.[16] Since epididymal development is dependent on androgen stimulation, it is speculated that closure of the PV is also regulated by androgen. Another suggested mechanism to account for the persistently patent PV is the failure of smooth muscles in the PV to regress. Normally, these muscles disappear after taking part in the descent of the testis, a process that appears to be regulated by the autonomic system. In patients with a hernia, the muscles fail to undergo apoptosis and maintain the patency of the PV.[17–20]

In the female fetus, the ovaries descend in a similar manner, except that the process is halted in the pelvis. The cranial portion of the gubernaculum forms the ovarian ligament, and the caudal portion forms the round ligament, which runs from the uterus to the labia majora. It appears that the gubernaculum also plays a role in guiding ovarian descent.[21] Only rudimentary development of the PV occurs, forming the canal of Nuck.

Presentation and Diagnosis

Children with a hernia or hydrocele often present with a history of a painless lump or bulge in the groin, scrotum, or labium (Figure 77.1). In younger children, this bulge may be more obvious while the child is crying, straining, or doing maneuvers that increase abdominal pressure. In older children, the hernia or hydrocele often gets larger during the day and smaller at night or during time of recumbency. Occasionally, a child may present with symptoms similar to those of acute testicular torsion, resulting from torsion of the hernia sac.[22,23] Approximately 10% of patients with an inguinal hernia present to medical attention with symptoms of bowel obstruction, such as nausea, vomiting, abdominal distension, and localized or generalized abdominal tenderness.

On physical examination, bowel can be palpated or heard during manipulation of the inguinal or scrotal bulge in patients with a hernia. Occasionally, a silk glove sign can be detected on exam, as the layers of PV can be felt around the spermatic cord, feeling like silk rubbing on silk. It has been suggested that the silk glove sign is not due to an empty hernia sac but the hypertrophied cremasteric muscle fibers.[24] Unfortunately, this physical finding is very inaccurate in the absence of finding an obvious hernia or hydrocele.[25] It should be noted that in most patients with a hernia, there are no findings on physical examination, and the diagnosis is dependent on the clinical history alone.

Typically, a nontender bluish discoloration to the scrotum and a soft mass around the testis are noted in patients with a hydrocele. In others, a painless mobile cystic swelling may be found anywhere along the spermatic cord. Termed a cord or encysted hydrocele, it is not reducible and can often be confused with a hernia.[26] Rarely, a child may present with an abdominoscrotal hydrocele in which a scrotal hydrocele has a dumbbell-shaped extension through the internal ring into the abdomen that forms an intra-abdominal cystic mass. In most patients,

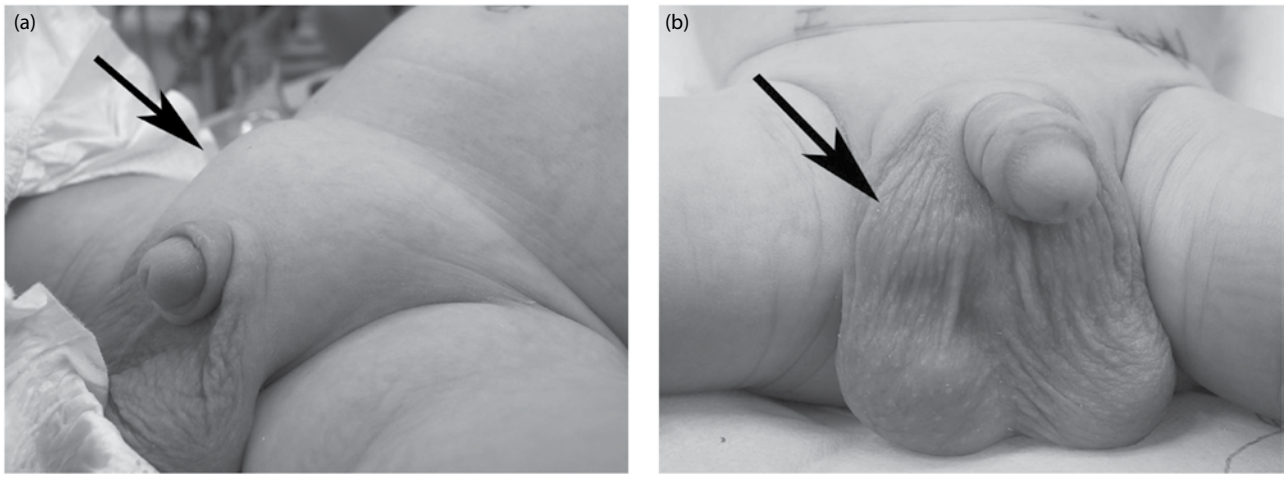

FIGURE 77.1 On physical examination, a bulge can be seen in the groin (a) or in the scrotum (b), distinct from the testis in infants with an inguinal hernia.

the hydrocele contains an exudative fluid. However, other fluid types have also been found in association with a hydrocele. A meconium hydrocele results from an in utero perforation of bowel and subsequent inflammation and calcification of the meconium.[27] A pyocele can develop in association with acute appendicitis,[28,29] infection of the epididymis or testis, tuberculosis peritonitis,[30,31] or primary bacterial infection.[32] A pneumocele may develop as a consequence of necrotizing enterocolitis or other causes of bowel perforation.[33] A hematocele can form as a result of blunt abdominal trauma with associated splenic injury or scrotal injury.[34] A hydrocele may also contain ascites fluid, such as bile, chyle, urine, cerebrospinal fluid in patients with a ventriculoperitoneal shunt, or dialysate fluid in patients on peritoneal dialysis. Hydrocele may also occur in girls, arising from the canal of Nuck.[35]

Being able to distinguish a hernia from a hydrocele on physical exam is often difficult. It has been suggested that transillumination may be used to identify a hydrocele (Figure 77.2). However, it should be noted that since bowel fluid and air will transmit light in a manner similar to that of hydrocele fluid, this finding is not reliable. When a scrotal mass is easily reducible, this suggests that there is a large patent PV representing either a hernia or a large communicating hydrocele. In contrast, when the mass is not reducible, it is likely to represent either a noncommunicating hydrocele, one with a small patent internal ring, or an incarnated hernia.

In most patients with a hernia or hydrocele, the diagnosis can be made by clinical history and physical examination. In those few patients in whom the diagnosis cannot be well established, further radiological examination may be helpful in establishing the diagnosis. In addition, when the testis cannot be palpated on physical examination, further radiological imaging is required to rule out potentially serious pathologies, such as undescended testis, infection, or testicular cancer. Ultrasonography (US) is widely utilized in evaluating inguinal and scrotal pathology. In patients with a hernia, fluid or air-filled loops of bowel may be identified in the inguinal canal or scrotum. When there is omental herniation, hyperechoic masses can be seen. However, it should be noted that US often fails to detect herniated bowel loops since the herniation is often periodic. In the absence of finding bowel or fluid in the inguinal canal, an increased groin width, as measured by US (7.2 ± 2.0 mm compared with 3.6 ± 0.8 mm in normal inguinal canal), has been used as diagnostic criteria for a hernia.[36] In contrast, a hydrocele on US can be identified by identifying fluid in between tunical layers and the normal testis or epididymis. The hydrocele may contain loculations. Fine-particulate matters seen on US may represent pus or blood, while calcification (seen as hyperechoic masses) suggests the presence of meconium.

Aside from US, other imaging techniques are seldom helpful in the diagnosis of a hernia or hydrocele. A kidney, ureter, and bladder (KUB) may demonstrate air or calcification in the scrotum, suggesting the presence of a pneumocele or meconium hydrocele, respectively. Herniography has been utilized in the diagnosis of a hernia.[37] Iothalamate solution (60%) is injected into the peritoneum. The patient is placed in an upright position for 10 minutes; a KUB or a computed tomogram (CT) is obtained to identify contrast lining the patent PV or hernia sac.[38,39] Because of potentially serious complications, such as bowel injury, contrast reaction, and peritoneal irritation, its use is limited to special circumstances, such as evaluating chronic groin pain.[40,41]

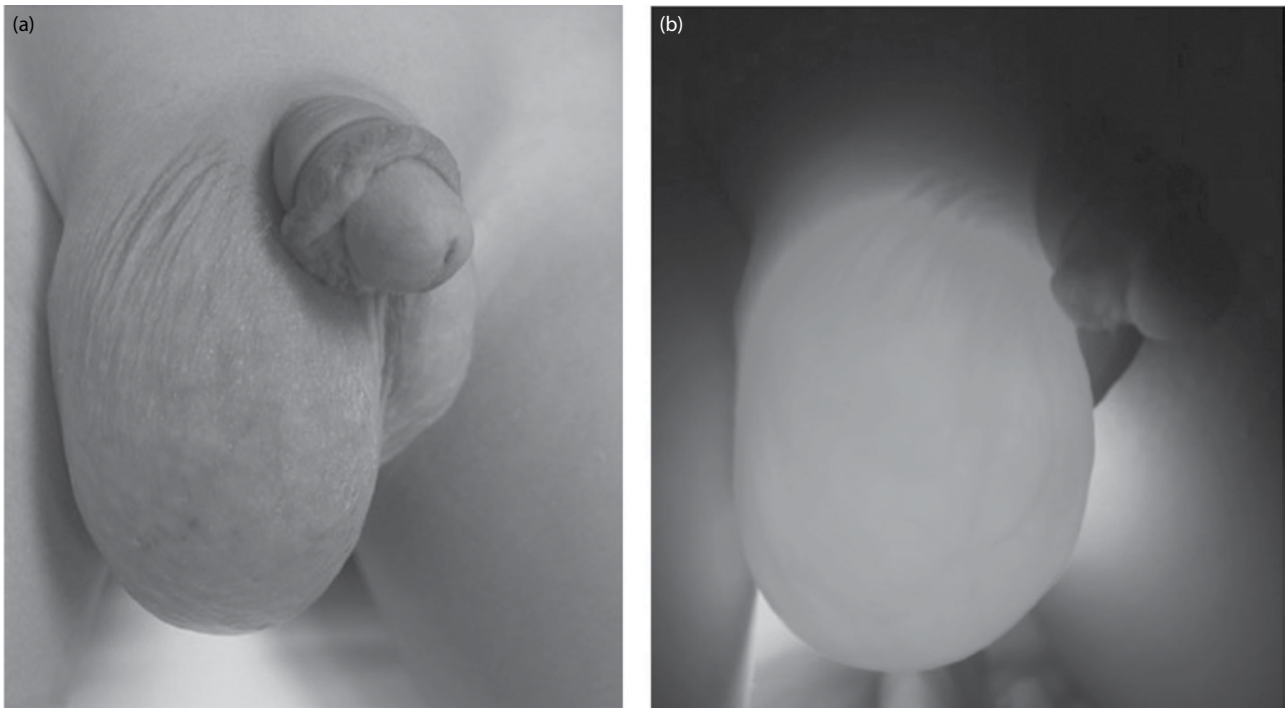

FIGURE 77.2 On physical examination of a boy with a hydrocele, scrotal swelling can be seen involving the testis (a), and it does transilluminate (b).

Management and Techniques

Hernia Repair

Currently, there is no effective medical management of a hernia; the use of a truss is primarily of historical interest. Since inguinal hernia is likely to persist indefinitely, it is recommended that children who are diagnosed with an inguinal hernia undergo surgical repair to prevent bowel incarceration and potential testicular atrophy. This is of particular importance in premature infants and neonates, who are at higher risk of developing bowel incarceration while waiting for surgery.[42] In extremely premature infants, hernia repair can be safely deferred until the child is ready to be discharged from the neonatal unit.[43] It is reported that the success rate for hernia repair approaches 99%.

For the parents, one potential concern in the surgical management of hernia or hydrocele is the possible harmful effects of general anesthetics on the brain development of the infants. Animal studies suggest that early exposure to anesthesia may impair normal neuronal development. However, epidemiological studies in children exposed to surgery with anesthesia early in life are contradictory and can neither rule out nor confirm anesthetic-related neurotoxicity.[44] Currently, most experts believe that general anesthesia within the first 1–2 months should be reserved for emergencies, while elective surgery after 3–6 months is safe. The type of surgical repair is dependent on the type of inguinal hernia. The direct inguinal hernia requires reconstruction of the floor of the inguinal canal with or without the use of prosthetic materials, such as polypropylene, Dacron, or polytetrafluoroethylene (PTFE). Since it is an uncommon type of hernia in children, a review of all types of direct inguinal hernia repair is beyond the scope of this chapter but is provided by Read.[45] Repair of the indirect hernia can be approached with either an open or a laparoscopic technique. Czerny and Banks was credited with introducing the concept of high ligation of the hernia sac in 1877. In brief, an inguinal incision, which is preferably hidden in a skin crease, is made approximately one-third the distance from the pubic tubercle to the anterior iliac spine. Scarpa's fascia is next incised, and the external oblique fascia is exposed. The shelving edge of the fascia is then defined with blunt dissection; this will allow for easier closure of the external oblique fascia later. To expose the inguinal canal, the fascia is incised along the direction of the fibers, parallel to the shelving edge over the external ring. After identifying the spermatic cord, the cremasteric muscles are separated to expose the hernia sac, which is located superior medial to the vas and testicular vessels. The hernia sac is carefully dissected from adjacent structures and divided between hemostats (Figure 77.3). The hernia sac is next freed proximally to the internal ring, where it is ligated with absorbable sutures. The distal portion of the hernia sac is opened down to the testis to prevent hydrocele formation. A similar technique is done for the repair of inguinal hernia in girls (Figure 77.4). It is important in these patients to open the hernia sac to ensure that there are no herniated

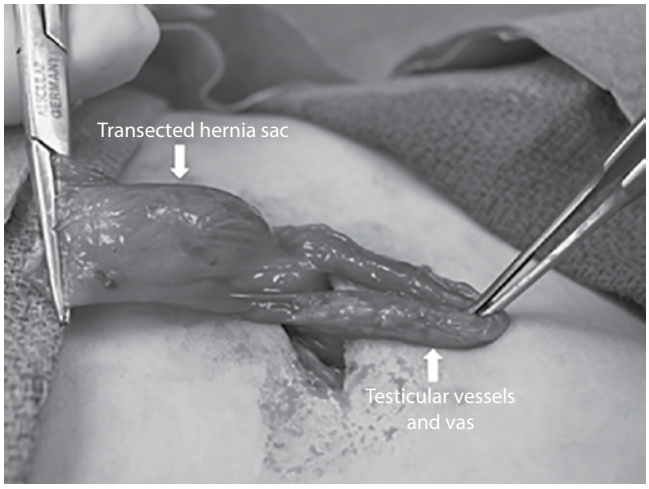

FIGURE 77.3 During the repair of an inguinal hernia, the hernia sac, which is located anterior medial to the spermatic cord, is carefully dissected away from the cord, ligated, and divided.

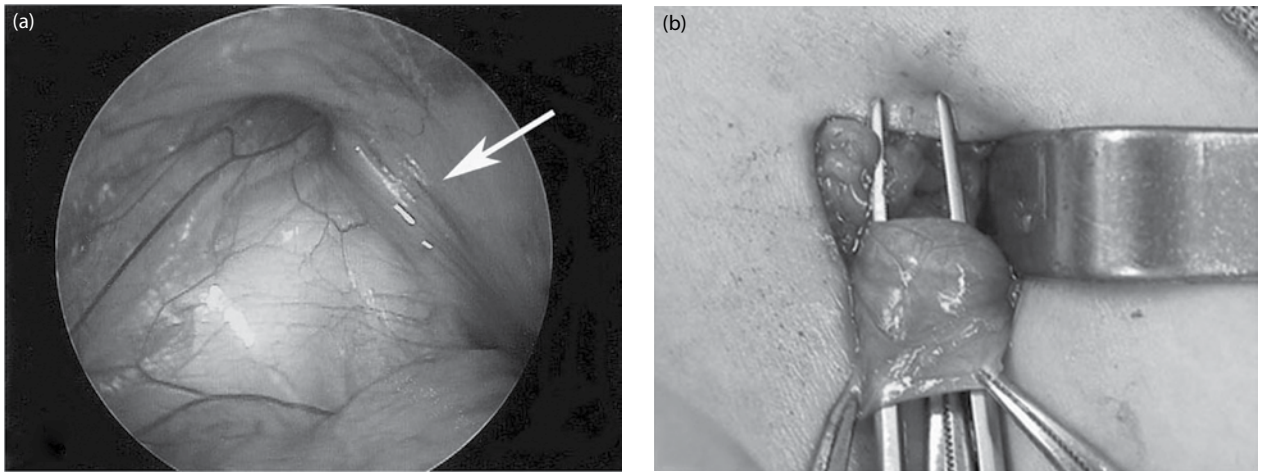

FIGURE 77.4 Inguinal hernia can also develop in girls. (a) On laparoscopy, an opened internal ring can be seen with the ovarian ligament (arrow) entering it. (b) On inguinal exploration, a hernia sac is identified. The hernia sac should be carefully examined to make sure that there are no structures herniating through the sac.

structures, such as gonads or fallopian tubes. Variations of this technique include approaching the hernia sac through a scrotal[46] or a low inguinal groove incision.[47] However, it should be noted that these approaches might limit surgical exposure to allow high ligation of the hernia sac near the internal ring.

The repair of the indirect hernia may also be performed by laparoscopy. The internal ring can be approached either transperitoneally or preperitoneally,[48] and the opening closed with a metal clip or sutures.[49] The surgical success rate using this technique is approximately 97%.[50,51] The laparoscopic approach is especially useful in patients with recurrent hernia. It allows for identification of the etiology of the recurrence, such as incomplete ligation of the hernia sac, the de novo development of a direct hernia, and the presence of other types of hernias, such a femoral hernia.[52,53] More recently, the use of needlescopic hernia repair has been advocated. In brief, a 1.7 mm needle laparoscope is introduced through the umbilicus to visualize the opened internal ring. Through a second port placed laterally, a grasper may be placed in the abdomen to help in the traction of the spermatic cord. A 2–3 mm incision is then made in the skin directly over the internal ring, and a suture is passed percutaneously anterolateral to the internal ring to perform an extraperitoneal high ligation of the hernia sac.[54] Long-term results and complication rates using this technique are not yet known.

Hydrocele Repair

Unlike hernias, hydroceles may resolve spontaneously during the first year of life. Thus, in the absence of a hernia, surgical treatment for hydroceles can be deferred and observation is warranted. In older children who acutely present with a hydrocele, the underlying etiology, such as epididymitis or orchitis, should be treated. If the hydrocele persists several months after treatment, surgical repair may be considered. In young children, the hydrocele repair is performed in a manner similar to that described for repair of the indirect hernia, since these patients are likely to have a patent PV. Particular attention should be paid to opening up the PV distally to testis to prevent recurrence of the hydrocele. In older children, the hydrocele repair can be performed through a midline or transverse scrotal incision since there is a low likelihood of a patent PV. The tunica vaginalis can be excised, everted (the bottle procedure), or imbricated (the Lord procedure). Sclerotherapy has been used in the treatment of hydroceles. The hydrocele is injected with a sclerosant such as tetracycline or polidocanol.[55] Complications include pain, long-term hazards of the sclerosant, and leakage of the sclerosant through a patent PV. In addition, recurrence following treatment is common. Consequently, sclerotheraphy is not recommended for children.

Potential Structures Encountered in the Hernia Sac during Surgery

Numerous structures can be potentially encountered in the hernia sac; therefore, great care should be taken when dividing the sac. Typically, the hernia sac may contain intestine (small bowel, large bowel, appendix, and Meckel diverticulum) or omentum. Occasionally, the bladder or intra-abdominal catheters, such as a CAPD catheter or a ventriculoperitoneal (VP) shunt, may herniate through the sac.[56] Less frequently, ectopic tissue such as that from the adrenal cortex,[57] spleen,[58] liver,[59] kidney,[60] and brain[61] can be found in the hernia sac. In a few rare cases (<0.1% of hernia repairs in adults and even less in children[62]), an unexpected discovery of a neoplasm is made during a hernia repair. Types of neoplasm found in the hernia sac include primary mesothelioma and liposarcomas,[57] extrarenal Wilms' tumor,[63] and metastatic cancer from the gastrointestinal tract, the ovaries, and the prostate.[8]

More frequently, the gonads and their associated structures may be encountered in the hernia sac. Despite having a palpable testis in the ipsilateral hemiscrotum, an additional testicle may be found at the time of hernia repair in boys with supernumerary testis[64] or cross-testicular ectopia. In approximately 2%–3% of phenotypic girls undergoing hernia repair, a testis may be found in the sac, suggesting the diagnosis of testicular feminization syndrome.[65,66] In these patients, the testis can be removed either after puberty to reduce the risk of germ cell malignancy (such as gonadoblastoma) or at the time of hernia repair to reduce the risk of virilization when the androgen insensitivity is not complete. An ovary can also be found in the hernia sac in 4% of girls undergoing surgery. Approximately 25% of these patients will have evidence of torsion effects or infarction in the herniated ovary.[67] Less often, genital duct structures are identified at the time of surgery or during pathological evaluation. Functional Wolffian duct derivatives, such an accessory vas or epididymis, may be seen separate from the spermatic cord. In patients with hernia uterine inguinale who have an anti–Mullerian inhibiting factor or its receptor defect, persistent Mullerian structures, such as a uterus, may be found in the hernia sac.[67–69] Due to the close relationship with Wolffian duct structures, great care has to be taken in excising the persistent Mullerian structures. In 2%–6% of the cases, nonfunctional Mullerian or Wolffian remnant structures can be identified in the hernia sac.[70,71] These structures are characterized by ciliated low columnar cells with occasional interspersed pale round cells, occurring singly, in small groups or in large clusters.[72] They are smaller than functional duct derivatives and lack significant muscular coats. Given the potential for finding various structures in the sac, some clinicians have recommended sending the hernia sac routinely for pathological examination. However, Miller et al.[73] observed that in their series of 456 patients, only 4 cases (0.88%) had unexpected findings on pathological evaluation of the hernia sac. None of these cases were of clinical significance (i.e., changed the patient management). The authors concluded that the routine histologic evaluation of inguinal hernia sacs in children is an unnecessary expense and should be reserved for select cases at the discretion of the surgeon.

Management of the Contralateral Patent Processus Vaginalis

In children who present with a unilateral hernia, much controversy exists as to the management of the contralateral side. Some surgeons recommend routinely exploring the opposite side for a patent PV, while others are more selective based on clinical criteria, such as age or sex.[74,75]

Some utilize further radiological imaging, such as US,[76] or perform diagnostic pneumoperitoneum[77] or laparoscopy through the umbilicus[78,79] or hernia sac[80,81] to diagnose a patent PV. Others recommend just observation for the development of a contralateral hernia. From autopsy studies, it is observed that the incidence of a patent PV is 90% in preterm infants, 80% in newborns, 60% in children less than 1 year of age, and 15%–30% in adults.[82,83] From studies in which the patency of the contralateral PV was assessed in children with a unilateral hernia, it is observed that the incidence of a patent PV is also age dependent. Approximately 60% of children less than 2 months of age who had a unilateral hernia had a patent contralateral PV. This incidence declines during the first 2 years of life and stabilizes at 40% in children from 2 to 16 years of age.[75,84]

Several studies have also observed that the incidence of a contralateral hernia developing following unilateral hernia repair ranges from 3.6% to 10% (an average of approximately 7%),[85–89] far exceeding the rate of a patent PV. Chertin et al. similarly found that the incidence of developing a contralateral hernia in 300 girls who presented with a unilateral hernia and underwent a unilateral repair was 8%.[90] Using a univariate analysis with the Cox regression models, Ikeda et al. observed that a left-sided hernia and a positive family history were significantly associated with the metachronous development of a contralateral hernia.[91] However, the incidence was at most 10%. Miltenburg et al. performed a meta-analysis of the risk of metachronous hernia in infants and children and found that there was a 7% risk of developing a contralateral hernia following unilateral repair.[92] Gender and age were not risk factors. Similar to the findings by Ikeda et al.,[91] there was an 11% risk of metachronous hernia if the original hernia was on the left side, a risk that was 50% greater than if the original hernia was on the right. Of patients who developed a metachronous hernia, 90% did so within 5 years, with a complication rate of 0.5%.[78] Based on these findings, it can be concluded that patients with a patent PV do not necessarily progress to develop a clinically apparent inguinal hernia. Concurrent management of a contralateral PV is of probable benefit in premature and young infants, where the risk of a second anesthesia is high, and in children with risk factors for hernia recurrence, such as cystic fibrosis or connective tissue disease. Interestingly, it was observed that in a study in which the parents were presented with the above issues and asked to choose between unilateral hernia repair only or with concomitant evaluation and repair of a contralateral patent PV for their child, 85% of the parents chose the latter.[93] Approximately 80% of those who chose the latter surgical option indicated that convenience was the primary motive in their choice, and only 19% had concerns about their child undergoing a second anesthesia if a contralateral hernia later developed.

Complications of Hernia or Hydrocele Repair

In general, the complication rate is higher in patients undergoing hernia repair than in those undergoing hydrocele repairs and in emergent compared with elective repair. The primary concern is associated with the anesthetic risk;[94] this is of particular significance in premature infants and those less than 3 months of age. Improvement in pediatric anesthesia techniques, such as the use of laryngeal mask[95] with caudal[96] or local anesthesia and the use of regional anesthesia in premature infants,[97] has greatly decreased the risk of potential anesthetic complications. Early complications associated with a hernia or hydrocele repair include local edema, hematoma, and wound infection. Early recurrence of inguinal or scrotal swelling may be due to a missed hernia or refilling of the potential space with fluid. Late complications include iatrogenic, upward displacement of the testis (incidence of 1% in children undergoing hernia repair);[98] paravesical abscess;[99] damage to spermatic cord; and recurrence. The incidence of spermatic cord injury during uncomplicated inguinal hernia surgery is approximately 1%, and less during hydrocele repair.[100] However, if the hernia is incarcerated, the risk of spermatic cord injury increases significantly to 6%–10%, with a subsequent testicular atrophy rate of 4%.[101] It is suggested that due to pressure, the bowel incarceration induces ischemia on the spermatic cord. The rate of recurrence following open hernia or hydrocele repair is approximately 1%–3%; however, it may be as high as 20% in premature infants undergoing repair.[45] Recurrence may be due to failure to dissect a complete sac, tearing of the sac, or slippage of sutures in ligating the sac. Moreover, in patients with recurrent hernia, other pathologies, such as connective tissue diseases, should be considered. Hydrocele formation following hernia repair with either an open or laparoscopic approach occurs in less than 1% of the patients.[50,51]

TESTICULAR AND APPENDICAL TORSION

Definition and Incidence

Normally, the tunica vaginalis covers the anterior surface of the testis, epididymis, and various distances over the spermatic cord. Attachment with the gubernaculum and scrotal wall posteriorly allows the testis to be fixed, preventing its twisting around the vascular mesentery. However, when these attachments are not secure, torsion of the testis may occur, leading to vascular compromise. Although testicular torsion can occur at any age, there is a bimodal distribution in the age of presentation, during puberty and during the neonatal period. More commonly in adolescents, testicular torsion involves torsion of the spermatic cord within the tunica vaginalis, an intravaginal torsion. Due to abnormal fixation of the testis and epididymis, the testis is allowed to freely hang within the tunical cavity. This "bell clapper" deformity allows the testis to adopt a horizontal position in the scrotum (Figure 77.5a). It is found in 12% of testes at postmortem, and frequently occurs bilaterally.[102] It is the most common etiology of torsion in adolescents, in whom rapidly increasing testicular mass associated with puberty increases the chance of the testis rotating. Intravaginal testicular torsion can also occur intermittently, spontaneously twisting and untwisting (Figure 77.5b). Torsion of an undescended testicle is an uncommon condition in adolescence and adulthood;

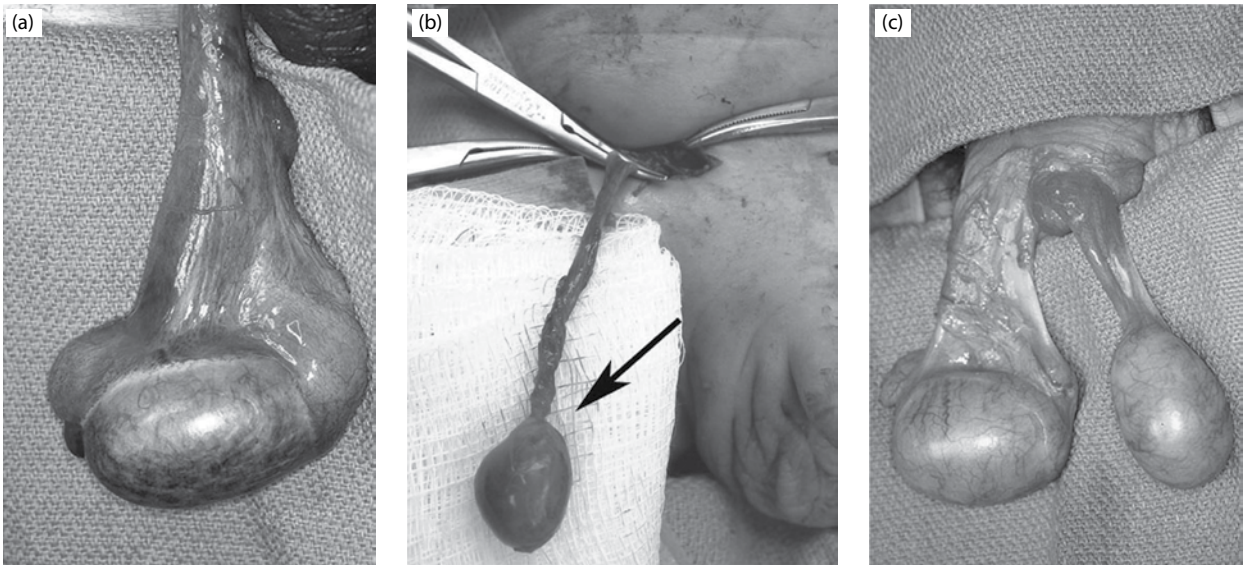

FIGURE 77.5 (a) In adolescents, testicular torsion occurs intravaginally, commonly due to the bell clapper deformity. (b) In neonates, testicular torsion occurs extravaginally, in which the entire cord is twisted about its axis (arrow). (c) In children with intermittent torsion, such as the one shown here, who presented with intermittent left testicular pain, a bell clapper deformity (left testis) is often seen on the affected side.

however, it is reported to occur more frequently than torsion of a normally descended testis. In a patient with pain and uncorrected cryptorchidism, a testicular tumor must also be considered in the differential diagnosis.[103]

Approximately 10% of all testicular torsions occur in newborns. In 70% of these patients, torsion occurs prenatally and is diagnosed at the time of birth. In the other 30% of patients, torsion occurs in previously normal testes.[104] Testicular torsion in newborns occurs primarily extravaginally. In the neonatal period, the descending or recently descended testis and its coverings are very mobile within the scrotum, creating a risk for the spermatic cord to twist en masse (Figure 77.5c). Multiparity, excessive uterine pressure, and a strong cremasteric contraction have been suggested as etiologic factors for extravaginal torsion.[105]

Torsion of the testicular appendages may also occur. The appendix testis is a vestigial remnant of the Mullerian system located on the upper pole of the testis. It is found in 90% of males and bilaterally in 60% (Figure 77.6a). Appendages may also be found on the epididymis (Figure 77.6b), epididymotesticular grove, or the cord itself. These appendages are remnants of the Wolffian system. Approximately 95% of the appendical torsions involve the appendix testis. The peak age of presentation is around 10 years.[106] It has been suggested that hormonal stimulation during pubertal development increases the size of the testicular appendages, making them more susceptible to twisting around their small blood supply. In a review of 100 boys less than 15 years of age who presented with acute scrotal pain, Melekos et al.[106] observed that 42% had testicular torsion and 32% had appendical torsion.

Presentation and Diagnosis

Children and adolescents who present with an acute painful scrotum require prompt evaluation. Timely and accurate diagnosis is required to prevent testicular loss. While the differential diagnosis is extensive (Table 77.1), the diagnosis can be determined based on history, physical examination, and limited laboratory and radiological evaluation. Typically, adolescents with intravaginal testicular torsion will present with acute onset of severe scrotal pain. In a series of 670 patients with acute testicular torsion, 89% of the patients presented with a complaint of acute-onset ipsilateral testicular pain.[107] The remaining patients presented only with pain referred to the ipsilateral lower abdomen, groin, or thigh. The majority of these patients were later found to have torsion in the undescended testis. Associated trauma and recent exercise were seen in 4% and 10% of the patients, respectively. About 11% of the

TABLE 77.1 Differential diagnosis for acute or subacute scrotum

Testicular torsion
Appendical torsion (testis or epididymis)
Epididymitis/epididymo-orchitis
Inguinal hernia (reducible or incarcerated)
Hydrocele
Trauma (mechanical, burns, or animal/insect bite)
Testicular neoplasms
Spermatocele
Varicocele
Dermatologic lesions
Inflammatory vasculitis (Henoch–Schonlein purpura)
Idiopathic scrotal edema
Referred pain

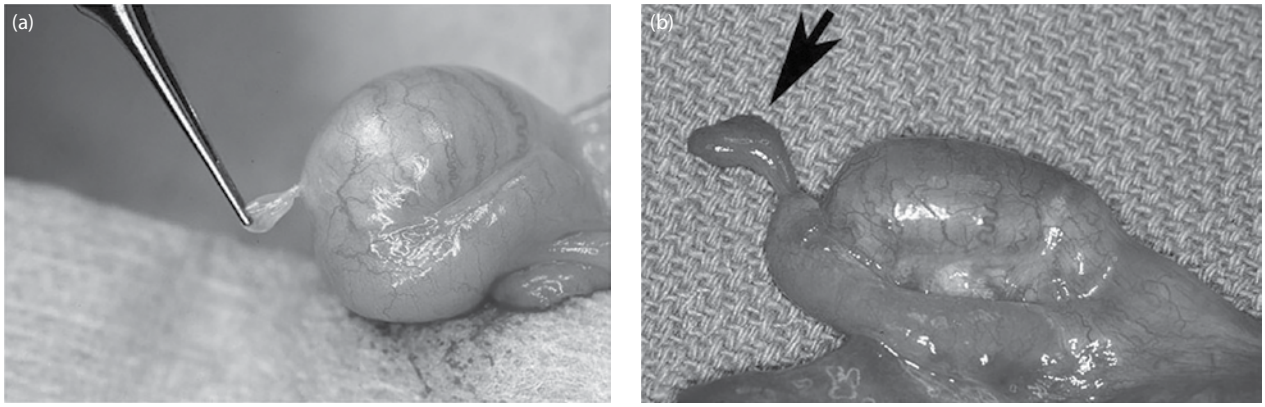

FIGURE 77.6 Acute testicular pain can also be due to torsion of the testicular appendages, such as the appendix testis (a) and appendix epididymis (b).

patients were woken from sleep with the pain. Nausea and vomiting were associated with testicular torsion in 39% of the patients, while urinary symptoms, such as dysuria and urgency, were usually absent (less than 5%). Interestingly, 36% of the patients had a previous history of testicular pain or swelling. A prior history of ipsilateral orchidopexy does not exclude the diagnosis of testicular torsion. Inadequate fixation and the development of single adhesions forming an axis for the testis to twist have been observed in patients with a prior history of orchidopexy but presenting with a recurrent testicular torsion.[108] Physical examination of the torsed testis is often very difficult due to the severity of the pain. Important signs of testicular torsion include a firm testicle high riding in the scrotum, an abnormally transverse orientation of the testis, and the absence of a cremasteric reflex.[109] In many cases, acute hydrocele or marked scrotal edema develops when several hours have passed since the onset of the scrotal pain. Fever and an elevated white blood cell count are seldom associated with testicular torsion. Intermittent testicular torsion has a presentation similar to that of intravaginal torsion, except that the episode is self-limited, with resolution of symptoms after the cord spontaneously untwists. Many who present with acute testicular torsion have a history of prior episodes consistent with intermittent testicular torsion. Those with intermittent torsion are likely to have normal physical exam at time of evaluation, when the pain has resolved. In contrast to those with intravaginal torsion, patients with extravaginal neonatal torsion typically present with painless swelling and scrotal discoloration. A firm testis with an associated hydrocele is often noted incidentally on newborn examination or during diaper change. Interestingly, associated scrotal erythema is not often present, but the overlying skin is discolored by the underlying hemorrhagic necrosis.

Patients with appendical torsion can also present with pain similar to that in those with intravaginal testicular torsion. However, the presentation for appendical torsion can be quite variable, from an insidious onset of scrotal discomfort to acute severe scrotal pain. Consequently, it is often difficult to differentiate appendical torsion from other causes of acute scrotum. At the earlier stages, the pain may be localized to the upper pole of the testis or epididymis, and a firm nodule can sometimes be palpated in this region of the scrotum. The pain is often more of a gradual onset rather than developing acutely, and associated symptoms such as nausea, vomiting, and abdominal pain are very infrequently associated with the testicular pain. On physical examination, the infarcted appendage can be seen through the scrotal skin as a blue dot; this is considered pathognomic for appendical torsion. However, the "blue dot" sign is only seen in approximately 20% of patients with an appendeal torsion.[106] In the latter stages, scrotal wall edema and erythema can develop, distorting the physical examination. The cremasteric reflex is usually preserved and the testis remains mobile.

In those who are suspected of having testicular torsion on a clinical basis, prompt surgical exploration is mandatory. Adjunctive radiological tests should only be obtained when their purpose is to confirm the absence of testicular torsion so that surgical exploration can be avoided. These tests are also of use in patients in whom the duration of symptoms suggests a nonsalvageable, dead testis if torsion is the cause. In these limited cases, color or power Doppler US or ^{99m}Tc-radioisotope scintigraphy may be obtained to evaluate testicular blood flow. Both of these tests are dependent on the availability of the equipment and personnel. False negatives can occur with any of the above modalities. The choice of which modality to utilize varies depending on the institutions, local experience, and availability and reliability of the tests. Color Doppler US studies can assess the anatomy of the scrotum and its content, while determining the presence or absence of testicular blood flow (as measured by velocity). The sensitivity of color Doppler US is reported to be as high as 90%, with a specificity of 99%.[110] However, caution must be used in the interpretation of these studies; almost 40% of patients, especially those younger than 8 years of age, may fail to demonstrate flow on the asymptomatic side.[111,112] Power Doppler US measures blood flow by detecting the number of red blood cells, as opposed to the velocity of flow. Although blood flow is more consistently detected in younger children with power Doppler,[111] evidence from animal studies suggests that power Doppler and color Doppler are equally efficacious in the detection of torsion.[113] Radionuclide imaging was originally the study of

choice for ruling out testicular torsion.[114] However, it only allows for the assessment of blood flow. Its positive predictive value has been reported to be around 75%, with a sensitivity of 90% and a specificity of 89%.[111] Hyperemia of the scrotal wall can give false impressions of testicular blood flow. In addition, it is difficult to image children with small scrotal sacs or testis using this study.

Effects of Unilateral Torsion on Testicular Function

Ischemia damage from torsion is related to the duration of the torsion and number of turns on the spermatic cord. Studies in dogs have demonstrated that all spermatogenic and Sertoli cells are not viable after 6 hours of testicular ischemia, and all Leydig cells are lost after 10 hours of ischemia.[115] However, in humans, severe testicular atrophy can be seen as early as 4 hours, when the degree of torsion is greater than 360°.[116] It is likely that when the cord is torsed greater than 360°, the artery becomes completely occluded. In contrast, when the torsion is less than 360°, arteriolar stasis develops secondary to venous occlusion and edema. In general, testicular atrophy is rare before 8 hours of torsion but is common after this time period.[117] The mechanism of testicular damage appears to be related to a combination of ischemia and reperfusion injury, resulting from activation of the xanthine oxidase system in parenchymal cells or from leukocytes adherent to the reperfused venule walls.

The effects of ischemia do not seem to be limited to the torsed testis. In patients who had treatment of testicular torsion within 4 hours of the onset of symptoms, half of the patients had abnormal semen analysis in follow-up, suggesting injury to both testes.[117] Studies in rats have confirmed that unilateral torsion can induce bilateral testicular damage and reduced fertility.[118,119] Several mechanisms have been suggested to explain these observations, including an immunological cause, congenital dysplasia, and damage of the normal testis by reflex vasoconstriction. It is suggested that torsion disrupts the normal blood–testis barrier, allowing the release of sperm antigens from the damaged testis. The antigens induce formation of autoantibodies, which then can attack the unaffected testis. In rats, it has been demonstrated that orchidectomy of the torsed testis, treatment with perioperative antilymphocyte globulin and splenectomy,[120] or administration of immunosuppressants such as steroids and cyclosporine[121] can prevent contralateral testicular damage. Similarly, in humans, patients with torsion for greater than 24 hours who had undergone an orchidectomy are more likely to have normal semen analysis than those in whom the torsed testis was left in place.[117] While there is ample evidence in animal studies that damage of the contralateral testis is mediated by an immune response, direct evidence in human studies is lacking. Anti-testis antibodies have been found only in approximately 10%–20% of patients who had a testicular torsion.[122,123] However, their presence does not correlate with infertility or with any testicular exocrine or endocrine dysfunction. An alternative explanation for the observed abnormal semen parameters in patients with unilateral torsion is the presence of underlying congenital dysplasia in the unaffected testis. Biopsies from the contralateral testis at the time of treatment for unilateral torsion demonstrate abnormalities such as desquamation of the germinative epithelium, atrophy of the Leydig cells, and malformation of spermatoblasts in 88% of the cases.[124] The presence of these abnormalities so soon after the onset of torsion suggests that there may be preexisting underlying pathology in contralateral testis. However, this explanation does not explain the consistent correlation between the duration of torsion and total sperm count, unless the damage is compounded by another mechanism.[125] The most recent explanation of the observed damage in the nontorsed testis is that it is caused by ischemia induced by reflex vasoconstriction. In animal studies,[126–128] unilateral testicular torsion induces an immediate and progressive decrease in blood flow to the contralateral testis and a gradual increase after detorsion. Like the affected side, the contralateral testis can be damaged by a combination of ischemia and reperfusion injury. The effect of torsion on contralateral testicular blood flow appears to be mediated by sympathetic nerve discharges from the genitofemoral nerve.[129]

Several studies have suggested that testicular damage after torsion could be limited by cooling of the testes, suppressing immune-mediated damage, and chemical sympathectomy to prevent reflex vasoconstriction. In animal studies, external cooling of the testis can delay the effects of ischemia for a few hours.[130] In addition, verapamil, surfactant, allopurinol, platelet-activating factor inhibitors, and hyperbaric oxygen have been used in an attempt to decrease reperfusion injury.[121,131,132] Similarly, immunosuppression with steroids, cyclosporine, and azathioprine has also been used in reducing testicular damage induced by an immune response.[133] Drugs such as capsaicin, 6-hydroxy dopamine hydrobromide, guanethidine monosulfate, and nitric oxide have been shown in animal studies to reduce testicular damage by preventing vasospasm and hypoxia in the contralateral testis.[134,135] Apart from hypothermia, the other methods of limiting testicular damage following unilateral torsion have been used in humans.[136]

Treatment

When suspected with testicular torsion, the patient should be taken to surgery without delay. Manual detorsion may be tried if surgical intervention cannot be done for a period of time. The testis should be turned caudal to cranial, and medical to lateral.[137] If the first attempt is unsuccessful, the testis should be turned in the opposite direction. If the detorsion is successful, the pain should resolve immediately. However, this process is often very painful, and manual detorsion may not completely correct the obstructed blood flow. Consequently, surgical intervention is still required following manual detorsion.

Fixation can be accomplished by securing the testis to the septum or placement into a dartos pouch. For transseptal fixation, the scrotum is opened through an incision in the median raphe. For the pouch fixation, the incision is made transversely following the skin creases of the scrotum. When using the latter method, the dartos pouch is made after the skin is incised. The tunica vaginalis is then

entered, and the testis is examined. The spermatic cord should be detorsed to restore blood flow. The affected testis should be placed in a warm sponge and observed for several minutes to determine viability. If it is nonviable, then the necrotic testis should be removed. Exploration of the contralateral testis should also be performed, and in all cases, the contralateral testis must be fixed. The testicles can be fixed to the median septum with 3–4 fine, nonreactive, and nonabsorbable sutures. These sutures can be brought through the septum, enabling the contralateral side to be fixed concurrently. Alternatively, a dartos pouch is created and fixation relies on scarification of the testis. The tunica vaginalis is everted and the testicle placed into the dartos pouch. A nonabsorbable suture is then used to secure the dartos tissue around the cord. This technique is advantageous in that complications such as abscess formation and tubular atrophy are uncommon. In addition, there have been no reported cases of recurrent torsion with this technique. Intermittent torsion is corrected using either of the above techniques on a semiemergent basis. Due to the effects of torsion on the function of the affected and unaffected testis, these patients will require further follow-up care to evaluate for infertility.

The treatment of neonatal torsion is controversial. Some suggest that surgical exploration is unnecessary, while others advocate immediate surgical exploration and fixation of the contralateral side. It is rare to salvage the affected testis in a patient with unilateral neonatal torsion; out of more than 30 cases of bilateral neonatal torsion reported in the literature, only two testicles have been successfully salvaged.[138] Important reasons for exploration are to exclude tumor and prevent possible unilateral torsion from becoming bilateral anorchia.[104] In the rare case of bilateral neonatal torsion, a more conservative approach can be taken. The newborn's general condition and anesthetic considerations should be evaluated to determine whether to proceed with surgical intervention.

The treatment of twisted testicular appendages is nonsurgical, if the diagnosis is certain. Conservative therapy with limitation of activity, scrotal elevation, and administration of nonsteroidal analgesics is highly effective. Most of the symptoms will dissipate once the acute changes of acute necrosis resolve. In rare instances, surgical exploration may be undertaken if conservative management fails. Simple excision of the torsed appendage is curative. Although an asymptomatic appendage is likely to be present on the contralateral side, exploration of the unaffected testis is not indicated. Some have advocated surgical treatment for the management of appendical torsion for these patients, as they seem to recover more rapidly and return to normal activity quicker than those treated conservatively.[139]

VARICOCELE

Definition and Incidence

A varicocele is caused by abnormal dilation of the internal spermatic vein and the pampiniform plexus of the testis. There are three primary vascular supplies to the testis: the internal spermatic, the vassal, and the cremasteric artery and vein. At testicular levels, there is free communication between the arteries. The pampiniform plexus is formed from veins providing the drainage from the testis and epididymis. As this plexus courses toward its drainage into the renal vein on the left and the inferior vena cava on the right, it becomes the internal spermatic vein. Like the arteries, there is free communication between the pampiniform plexus and the vassal vein, which drains via the inferior vesical vein into the hypogastric vein, and the cremasteric vein, which drains via the inferior epigastric vein into the external iliac vein. In addition, the distal portion of the pampiniform plexus is also drained via the anterior scrotal vein into the femoral vein.

A varicocele is rarely seen in boys less than 10 years of age.[140] Its incidence rapidly increases between 10 and 15 years of age, and it is seen in approximately 15% of male adults.[141] There appears to be a causal relationship between the pubertal development and varicocele formation. Varicocele may be classified by size during examination with the patient standing: Grade I varicocele is not visible but becomes palpable during the Valsalva maneuver, Grade II varicocele is easily palpable on exam without the need for the Valsalva maneuver, and Grade III varicocele is clearly visible on exam. Grade I varicocele is seen in approximately 9% of adolescent males, while Grade II is seen in 4% and Grade III in 2%.[142] The true incidence of varicocele may be underestimated since many adolescent males do not routinely undergo proper testicular examination in the upright position. Approximately 90% of varicoceles detected are found on the left side, while bilateral varicoceles occur in 2%–10% of the cases. An isolated, right-sided varicocele is uncommon, and its presence should raise the suspicion of a pelvic mass, compressing venous return.

Etiology and Pathophysiology

There are many theories as to the etiology of a varicocele. It is speculated that there are incompetent or absent valves in the left spermatic vein, which allows retrograde blood flow into the pampiniform plexus.[143] It also has been hypothesized that the anatomic differences between the left and right spermatic veins (with the left being longer and having a right-angle insertion into the left renal vein) allow for preferential transmission of higher hydrostatic pressures to the left pampiniform plexus. Alternatively, it has been suggested that a varicocele develops as a consequence of the left renal vein being compressed as it passes between the aorta and the superior mesenteric artery. However, this "nutcracker effect" has not been seen clinically.[144] Finally, it is hypothesized that a varicocele develops from abnormal embryonic transformation of the primary venous system into a secondary system. The inferior vena cava is formed as the subcardinal, the posterior cardinal, and the supracardinal veins involute. Disordered involution may cause a persistence of intercardinal anastomoses that could lead to the formation of the varicocele.[144]

While the etiology of a varicocele remains unclear, its effect on the testis is well documented. Biopsies from the testes of men with unilateral varicocele demonstrate incomplete maturation arrest at the spermatid and spermatocyte levels.[145,146] In addition, there is decreased

spermatogenesis and seminiferous tubular thickening with decreased tubular diameter. Interestingly, these changes are seen in both testes but are more severe on the varicocele side.[145] It has also been observed that there are changes in the other components of the testis. Leydig cell hyperplasia is seen in association with varicocele. Its presence can be used for prognosis, since the pregnancy rate was observed to be decreased from 40% to 5% in men with a varicocele who have Leydig cell hyperplasia on testicular biopsy.[147] Sertoli cell abnormalities have also been reported in men with varicocele. On light and electron microscopy, spermatids are seen to be maloriented relative to Sertoli cells, and Sertoli–germ cell junctional complexes appear to be structurally abnormal.[148] Finally, the testicular microvasculature is also affected in adolescents and men with varicocele, in which proliferative endothelial lesions in the capillaries are seen. These vascular lesions precede the testicular changes and are reversible with surgical correction.[149]

Varicocele is also associated with specific biochemical changes. It has been observed that there is decreased intratesticular testosterone concentration in some adult men with varicocele.[150] It is not surprising that this decrease correlates with impaired spermatogenesis and Leydig cell changes in men with varicocele.[150,151] Similarly, a decrease in serum testosterone has been noted in some men with bilateral Grade III varicoceles.[152] However, this observation is not seen in patients with other grades of varicocele.[153] Inhibin B is a glycoprotein produced by Sertoli cells and can potentially serve as a marker of Sertoli cell function in patients with varicocele. It is observed that serum inhibin B levels tend to be positively correlated with sperm concentration in some patients.[153,154] In comparison, it is more consistently observed that men[155,156] and adolescents[157] with varicocele have elevated gonadotropic hormones such as follicle-stimulating hormone (FSH). In addition, an excessive gonadotropin (in particular FSH) response to gonadotropin-releasing hormone (GnRH) is seen in some adolescents with varicocele. In one study,[158] it was observed that 31% of adolescents with a unilateral varicocele had an abnormal response to GnRH stimulation, and 75% of those with testicular hypotrophy of greater than 3 mL differential had an abnormal response. However, it should be noted that 54% of those who did not have elevated FSH and luteinizing hormone (LH) in response to GnRH stimulation also had hypotrophy. Aragona et al.[159] observed a correlation between abnormal testis histology and an exaggerated response to GnRH. This abnormal GnRH response appears to be limited to those with Tanner stage V. Approximately 40% of the Tanner stage V had an exaggerated response to GnRH, while those with Tanner stage III and IV had no difference in LH or FSH response to GnRH.[160] Unfortunately, the use of GnRH as a predictor for the need for surgery is limited since it does not correlate with the grade of the varicocele, testicular hypotrophy, or fertility.[160,161]

Since 98% of the testicular mass is comprised of seminiferous tubules and germinal cells, it is not surprising that the histologic, deleterious effects of varicocele may be seen grossly by changes in testicular volume. The average size of the testis in an adult male is 24 ± 3 mL. Normally, there is no more than 2 mL difference. It has long been noted that the ipsilateral testis of patients with a unilateral varicocele can be significantly smaller than the contralateral side.[162] It should be noted, however, that in adult men, although a varicocele can cause significant ipsilateral testicular atrophy or hypotrophy, there does not seem to be a correlation between loss of testicular volume and fertility status in men with a left varicocele.[163] In adolescents, absolute changes in testicular volume cannot be used since the testis is growing during puberty. Consequently, the percent volume loss compared with the right side is utilized. Like adult men, adolescents with a unilateral varicocele may have a significant amount of testicular volume loss. It remains a topic of debate as to what percentage of volume loss is considered significant (10% vs. 25%).[164,165] Nevertheless, it has been observed that volume loss is seen in 34% of adolescents with Grade II varicocele and 81% with Grade III.[141] Several prospective studies[159,164,166] have demonstrated that in adolescents, the testicular volume either fails to increase or even decreases in the presence of the varicocele.

The effects of the varicocele can also be seen in the semen quality. A "stress pattern" can be observed in the semen of adults with a varicocele in approximately 90% of cases.[167] These characteristic changes consist of subnormal motility, an increase in immature forms, a shift from oval to tapered, and amorphous sperm forms.[168] These changes may worsen over time.[169] In adolescents, varicocele is associated with impairment in sperm motility and morphology with no significant difference in sperm counts.[170] Surgical correction of the varicocele in adulthood[171–173] or in adolescence[164,174–176] results in improved semen parameters. In the only prospective study,[177] the only improvement in sperm concentration was noted in adolescents with a unilateral varicocele who underwent surgical correction.

Several theories have been suggested to speculate on the etiology of how a varicocele induces these damaging changes to the testis. It is speculated that these changes may be mediated by increased venous pressure or retrograde flow of toxic metabolites from the adrenal gland. Currently, the most plausible theory is that a varicocele induces thermal damage to the testis. Intratesticular temperature is normally maintained at around 33°C–34°C. A countercurrent heat exchange between the blood coming down and the blood leaving the testis allows the testis to be maintained at a lower temperature. It is suggested that a varicocele disrupts this countercurrent heat exchange and induces testicular hyperthermia, which interferes with normal spermatogenesis.[178] This theory has been demonstrated in animal models of varicocele (reviewed by Turner[179]). In primates,[180] dogs,[181] and rats,[182] partial ligation of the left renal vein results in varicosity of the left spermatic vein and the pampiniform plexus. The surgically created varicocele induces bilateral increases in testicular blood flow and temperature, resulting in decreases in intratesticular testosterone and sperm output.[179] These effects do not appear to be immunologically or neurologically mediated[183] and are reversed with varicocelectomy.[184,185] The pathophysiology of varicocele is multifactorial, and none can independently explain the mechanisms of impaired spermatogenesis. It is likely that a combination of several factors affects spermatogenesis

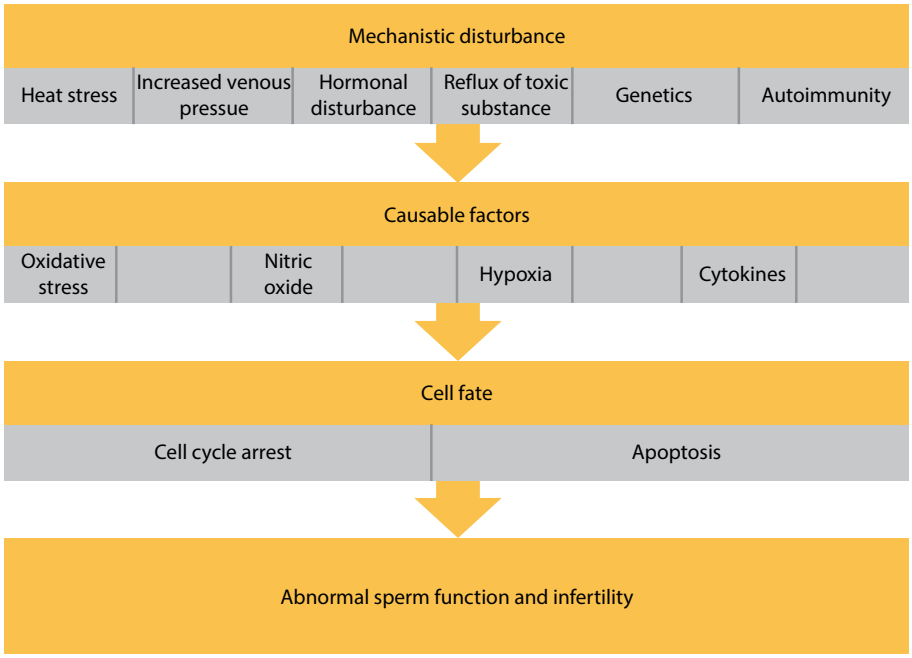

FIGURE 77.7 Summary of the potential etiology of abnormal sperm function and infertility in patients with varicocele.

and sperm function, and the relative involvement of these factors is different in each patient (Figure 77.7).[186]

Presentation and Diagnosis

The majority of the adolescents who present with a unilateral varicocele are asymptomatic; pain or a dull nagging ache is the presenting symptom in only approximately 3% of the patients.[187] The varicocele is usually detected on physical exam as scrotal swelling or mass. In evaluating for the presence of a varicocele, it is essential to examine the patient standing up and then perform the Valsalva maneuver. In addition, the testes should be carefully evaluated for their size and consistency. Several methods of testicular measurements, including rulers and calipers, orchidometers, and US, have been employed. Measurement using orchidometers such as the Prader, Rochester, and Takihara is readily available and inexpensive to perform; however, the accuracy of the measurement is highly dependent on the experience of the examiner. In comparison, measurement using testicular US is better correlated with actual testicular volume[188,189] but is more costly. Another advantage of using US in evaluating varicocele is its ability to pick up unexpected pathology, such as a retroperitoneal mass, intratesticular varicocele, or testicular mass. Intratesticular varicocele is seen on scrotal Doppler US as an intratesticular anechoic lesion with active Doppler flow. It is found in association with traditionally large extratesticular varicoceles and has been shown to resolve following spermatic vein ligation.[190]

When possible, a semen analysis should be obtained. Semen quality is a good indicator of testicular function in adults with varicocele. However, it should be noted that its use in adolescents with a varicocele has some potential limitation. Often, it is very difficult to obtain semen analysis in adolescents due to ethical concerns. In addition, normal semen parameters have not been well defined prior to sexual maturity; between 12 and 19 years of age, spermatozoa are absent, and semen parameters reach adult values 29–33 months after the onset of puberty.[191] Consequently, the interpretation of semen parameters is problematic in adolescents who are undergoing pubertal changes.

Serum measurement of FSH with or without GnRH stimulation may be potentially helpful in identifying those with testicular dysfunction induced by varicocele. However, as indicated previously, elevation in FSH levels and abnormal GnRH responses do not always correlate with abnormal semen parameters or fertility. In addition, not all patients with testicular dysfunction have elevated FSH or abnormal response to GnRH. Consequently, their routine use in evaluating adolescents with varicocele is limited.

In a very selected group of patients, further radiologic imaging may be utilized in the evaluation of a varicocele. Internal spermatic vein venography can delineate the anatomy of the varicocele; however, it is costly and invasive. Its use tends to be limited to selected patients with recurrent varicocele[192] or during intraoperative evaluation.[193] Another method in the evaluation of a varicocele is scrotal thermography to measure the scrotal temperature.[194,195] It is suggested that an observed increase in testicular temperature might identify those patients at risk for varicocele-induced testicular damage. Due to the lack of correlation with outcome, it is not commonly used in the US currently. Color Doppler US may also be used in evaluating for the presence of a varicocele (Figure 77.8). It is able to define the number of dilated veins, as well as the severity of dilation. However, with these various

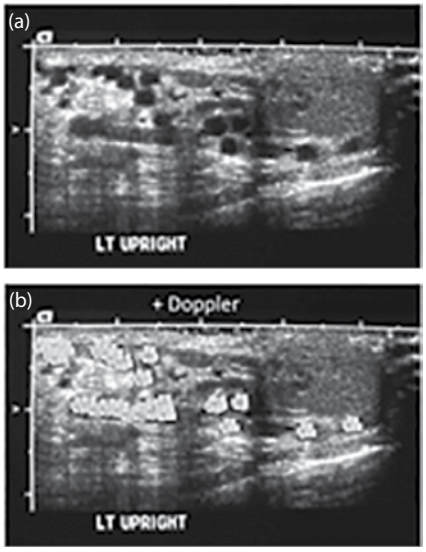

FIGURE 77.8 (a) On US, a varicocele can be identified by its "Swiss cheese" appearance. (b) Doppler US can demonstrate retrograde flow in the varicocele.

radiologic methods, many subclinical varicoceles can be identified (i.e., those that are not palpable on physical exam but are visualized with radiologic imaging). Using contact thermography and venography, approximately 7% of those with left-sided and 86% of those with right-sided varicocele are identified in the absence of findings on physical examination in adolescents who present for evaluation of a varicocele.[196] Because subclinical varicoceles are seen in approximately 60% of men attending fertility clinics, but also in 40% of fertile men,[197,198] the clinical relevance and thus importance of diagnosing subclinical varicocele are highly debated.

Treatment

Since 15% of adult men have a varicocele but only 20% of them have infertility, observation is a valid option in the management of patients with a varicocele. The risk in observing these patients is that some of them may demonstrate deterioration in the semen parameters and may progress to infertility. While surgical correction reverses these changes in at least 50% of adult men, in others it does not, suggesting a potential for developing irreversible damage. Consequently, early surgical correction of adolescent varicocele has been advocated. This recommendation is based on the assumption that adolescent varicocele is a progressive disease. In the only prospective longitudinal study in adults,[199] semen quality in men with untreated varicocele did not decline with time. However, most had semen quality at baseline that was worse than that of controls. In two studies of adolescent varicocele,[176,177] the authors observed lower semen quality in those who underwent varicocele than in those who were not treated. However, it should be noted that in the first study there was no sequential semen analysis, and in the second, the untreated group had similar semen parameters compared with the controls. In another study,[200] a group of adolescents with a unilateral varicocele was followed with serial exams, with a mean follow-up between the first and second exam of 16 months. There was neither an increase in varicocele grade nor a change in testicular volume differential over time, suggesting that perhaps adolescent varicocele is not a progressive disease. However, the limitations of this study are the length of the follow-up time and correlation with other parameters, such as semen analysis. Currently, there are no convincing data supporting or refuting the premise that adolescent varicocele is a progressive disease.

Consequently, with the goal of preserving fertility, it is important to identify those adolescents with varicocele who would benefit from early intervention. It is generally agreed on that an indication for surgical intervention is for symptoms such as pain. Although an uncommon complaint, 80%–90% of those who undergo varicocele repair will have resolution of their symptoms.[187] In addition, those adolescents with bilateral varicoceles may benefit from surgery since it is difficult to follow their testicular growth since both sides are affected. Similarly, in older patients with abnormal semen parameters on serial evaluation, surgical intervention would be indicated, allowing for potential improvement in semen parameters[175,176] and fertility.[201] In the era of assisted reproductive technology, studies[202,203] showed that the repair of varicocele often improves fertility success.

Other indications for varicocele repair in adolescents are more controversial. When semen analysis is not available, marked testicular volume differential is used as an indication for surgery. In adult men with a unilateral varicocele, testicular hypotrophy is associated with decreased total motile sperm counts.[204] However, there does not appear to be a correlation between the loss of testis volume and fertility status.[163] Nevertheless, surgical intervention does reverse the growth loss in adolescents with a unilateral varicocele.[170,175–177] Although it remains unclear whether varicocele repair solely for the purpose of reversing testicular hypotrophy improves future fertility potential, most would agree on this as an indication for intervention, in the absence of semen analysis. Size (i.e., grade) of the varicocele has also been suggested as a potential indication for surgical intervention. It is observed that in infertile men with Grade III varicocele, there was a greater improvement in sperm concentration and motility than in those with Grade I or II varicocele.[205] However, there was no difference in fertility rates in those with large or small varicocele who underwent repair.[205,206] Consequently, the grade of the varicocele in itself is not predictive of the need for surgical intervention. Similarly, the finding of a "soft" testis in association with the varicocele is not a strong indication for surgery. This finding is quite subjective and difficult to quantify, and consequently, there is a lack of data proving its value in predicting the need for early intervention. Finally, parental and adolescent preference often plays a role in determining the treatment of varicocele. They may feel that surgery may be of some psychological benefits, restoring normal scrotal appearance and allowing them not to worry about potential future complications.

Techniques of Varicocele Repair

There are several techniques that can be employed in the treatment of a varicocele, including percutaneous, open, and laparoscopic approaches. With percutaneous techniques, the dilated veins can be sclerosed with a chemical agent or occluded with coils or balloon. Access can be obtained percutaneously in a retrograde manner via the femoral or jugular vein or in an antegrade manner via the varicocele itself.[207,208] The advantages of the percutaneous techniques include being less costly and having a shorter recovery time than open surgery. In older patients, these techniques can be performed under local anesthesia, alleviating the need and risk of general anesthesia. However, it should be noted that in 15%–27% of the patients undergoing transvenous occlusion, the procedure could not be performed due to difficulties getting to the varicocele.[209] Potential complications include extravasation of contrast material, coil migration, postprocedure hydrocele formation (11%), and recurrence (5%).

Open surgical correction of varicocele has conventionally been the standard treatment of varicocele for many years. This treatment can be performed inguinally, retroperitoneally, or subinguinally. The Ivanissevich repair utilizes an incision in the inguinal region with the patient in reverse Trendelenburg position. The spermatic cord is exposed and mobilized in the inguinal canal. Under loupe magnification, all veins are ligated. The testicular artery, which may be dilated with warm saline or papaverine and identified visually or with Doppler US, can be spared or mass ligated with the veins. The advantage of this procedure is that it is easy to perform due to its anatomic familiarity and easy access to the cord. With this technique, there is a 3%–8.6% incidence of hydrocele postoperatively and a 16% recurrence rate in the treatment of adolescent varicocele. Both the hydrocele rate and recurrence rate can be reduced using microscopic dissection. Sparing the artery decreases the risk of hydrocele formation by sparing the lymphatic vessels surrounding the artery but increases the risk of recurrence due to missed venous connection.

The Palomo technique utilizes a muscle-splitting incision one to two fingerbreadths medial and anterior superior to iliac crest and the same distance above the estimated position of the internal ring, providing access to the retroperitoneum. The vessels are identified on the posterior aspect of the peritoneum; they may be better visualized by providing traction on the testis. As with the inguinal approach, the testicular artery can be ligated with the vein. The advantage of this technique is that above the inguinal canal, there are fewer venous branches requiring ligation, and that the vas and its associated vessels have separated from the rest of the cord, minimizing the risk of their injury. However, this approach often is more anatomically difficult and could miss scrotal or pelvic collaterals feeding into the varicocele. The incidence of hydrocele postoperatively is approximately 7%. Similar to that of the Ivanissevich repair, the rate of recurrence is around 11%–14% with sparing of the artery or 2% with not sparing the artery. Several studies[210] have demonstrated that ligation of the artery during Palomo repair can be safely performed and does not result in testicular atrophy.

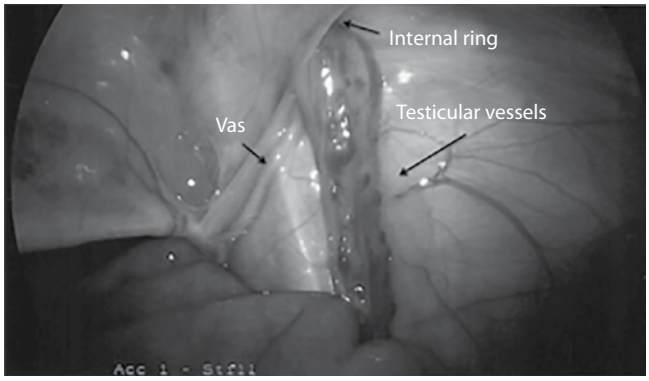

FIGURE 77.9 On laparoscopy, the spermatic veins can be easily identified in the retroperitoneum. Above the level of the internal ring, the vas and its vessels have separated away from the cord, minimizing its injury during the dissection.

The subinguinal technique utilizes a low transverse inguinal incision to expose the cord below the external ring. The external oblique aponeurosis is opened, and the testis is delivered out of the scrotum. Using an operating microscope, the artery and lymphatic vessels are identified and spared, while all the external spermatic veins and scrotal veins are ligated. By being able to identify and preserve the artery and lymphatic vessels, the incidence of postoperative hydrocele is very low (approximately 0.8%), with a 2.1% recurrence rate.[211]

Over the past decade, the laparoscopic approach to varicocele repair has gained much popularity. It can be performed with a transperitoneal or a preperitoneal approach. For the transperitoneal approach, an incision is made in the umbilicus and is extended down to the midline fascia. A pneumoperitoneum is created with a Veress needle or by the open Hassan technique. The abdomen is insufflated to 12–14 cm H_2O. Two additional ports are placed, one in the midline near the pubis and the second in between the other two. The position of the ports should allow the instruments to triangulate the work area. The patient is placed in a steep Trendelenburg position to allow the bowel to move out of the pelvis. Collaterals can be accessed by compressing on the main vein and squeezing the testis (Figure 77.9).[212] The vessels are mobilized from the peritoneum and are ligated. The artery may be identified with a Doppler US and spared.[213] After the completion of the procedure, the abdominal pressure should be reduced and the area carefully inspected for bleeding. The advantages of this technique include a shorter postoperative convalescence due to avoidance of a larger inguinal or abdominal incision, better visualization,[214] and the capacity to treat other associated problems, such as bilateral varicoceles or concurrent inguinal hernia.[215] The laparoscopic Palomo can be safely performed in patients who have undergone prior inguinal surgery without a risk of testicular atrophy.[216] The disadvantages include the requirement for general anesthesia, the cost, and the potential for bowel injury, bleeding, and peritonitis. Using this technique, the incidence of postoperative hydrocele is approximately 7% and the recurrence rate is 15%.[217–219]

Treatment of Postoperative Hydrocele and Recurrence

Esposito et al.[220] observed that the median incidence of postoperative hydrocele after varicocele surgery is about 12%. The incidence is higher after an artery-non-sparing versus -sparing procedure (17.6% compared with 4.3%). Interestingly, no difference in the postoperative hydrocele rate was observed between surgeries performed laparoscopically or those by open techniques. Hydroceles are infrequently detected within 6 months of varicocele repair, generally occurring after 6 months up to 3 years following surgery.[221] Total hydrocele regression occurs in approximately 80% of the patients following clinical observation or treated with simple scrotal puncture.[220] However, some may require open hydrocele repair.

Recurrence following varicocele repair is usually noted several months after surgery.[222] A lower recurrence rate is seen when performing mass ligation compared with artery-sparing surgery.[210,223] It is uncommon that recurrence is due to delayed recannalization.[222] Reoperation is indicated when the indications for the original surgery persist. Intraoperative venography may be helpful in defining collaterals that were missed during the initial surgery. This can be accomplished by placing the patient in a reverse Trendelenburg position and making a small scrotal incision to expose the dilated veins. The vein is cannulated with an angiocatheter, directed away from the testis. The catheter is then injected with 30% contrast at a volume of 1 mL/kg body weight. After an x-ray is obtained, the vein is flushed with normal saline solution. It is generally recommended that the cord should be approached at a higher level, in order to ligate the missed collaterals.

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CHAPTER
78

Minimally Invasive Management of Inguinal Hernias

Nicholas G. Cost and Paul H. Noh

INTRODUCTION

The first case of "minimally invasive surgery" in children was reported by Stephen Gans in 1971, in which he successfully verified a contralateral inguinal hernia via an endoscope introduced through the known hernia sac.[1] Therapeutic use of laparoscopy for pediatric inguinal hernia was then first reported by El-Gohary in 1997,[2] when he performed laparoscopic repair in girls by successfully everting the hernia sac into the peritoneal cavity and then using an endoloop to perform a "high ligation" (Video 78.1). Subsequently, Montupet and Esposito reported their experience in the mid-1990s of using laparoscopy to treat pediatric inguinal hernias in boys.[3]

In essence, a minimally invasive inguinal hernia repair in children is an adaptation of conventional herniotomy that fundamentally involves a high ligation of the indirect hernia sac. Broadly, laparoscopic pediatric inguinal hernia repairs can be classified into two approaches: (1) purely intracorporeal ligation and (2) laparoscopic-assisted extracorporeal ligation. In addition to traditional multiport laparoscopy, numerous novel minimally invasive techniques have been developed to approach the same problem in a variety of ways. These include "single-incision laparoscopy," such as laparoendoscopic single-site surgery (LESS) or single-incision laparoscopic surgery (SILS), or a wide array of endoscopically visualized extracorporeal ligations, such as subcutaneous endoscopically assisted ligation (SEAL) or percutaneous internal ring suturing (PIRS).

Regardless of the approach, the theory of minimally invasive approaches to the patent processus vaginalis (PPV) or indirect inguinal hernia in a child is the same, that is, reduction of any intraperitoneal contents and attempting to mechanically close the peritoneal connection. Herein, we aim to describe the various techniques of minimally invasive inguinal hernia repair in children, discuss their success rates, highlight the risk of complications, and lastly, mention special considerations in the management of these patients, such as hernia recurrence or bowel incarceration or strangulation.

TECHNIQUES OF THE VARIOUS MINIMALLY INVASIVE APPROACHES

The minimally invasive approaches to pediatric inguinal hernias can be broken down into two categories: (1) transperitoneal access with intracorporeal manipulation to close the hernia and (2) transperitoneal access for endoscopic visualization of extracorporeal management of the peritoneal communication. The various techniques approach dissecting out or ligating the hernia sac in a number of ways; however, they all share these two basic forms of minimally invasive access. A full discussion of laparoscopic access to the peritoneum is outside the scope of this chapter, but we discuss the details of patient positioning and the operative steps of each technique.

Transperitoneal Access with Intracorporeal Management of the PPV

This is the "traditional" technique of laparoscopic pediatric inguinal hernia repair used via multiport laparoscopy as it was initially described.[2,3] While there have been modifications in the number of ports used, the basic approach is the same, which involves transperitoneal access followed by high ligation of the hernia sac either with or without attempts at "disrupting" the peritoneal continuity with cutting or cautery. Patient positioning is as follows: using a supine position with the legs slightly spread, secure the patient to the table at the chest and legs using straps. During the surgery, it may be helpful to place the patient in a slight Trendelenburg position to allow for gravity retraction of the bowel (Figure 78.1), and it may also help to have the patient rotated slightly with the side of interest up. For this reason, we recommend testing the bed and patient positioning, once secured, prior to prepping and draping. After access is obtained, we prefer to use a 5 mm laparoscopic camera to visualize the inguinal ring of interest, as well as the contralateral inguinal ring, to evaluate for a concomitant bilateral PPV. Of note, any grossly appreciable patency will generally manifest itself with scrotal swelling at this point from transmission of the abdominal insufflation. One caveat is that in the setting of a clinical hernia, with a patency that does not extend into the scrotum, one may not observe scrotal distention with insufflation, but this does not rule out an open canal.

While there are recent descriptions of SILS duplicating a similar herniorraphy technique,[4,5] the traditional approach at this point would be to place additional ports as needed. Additional instruments are placed under direct vision via stab incisions without trocars. We prefer to use

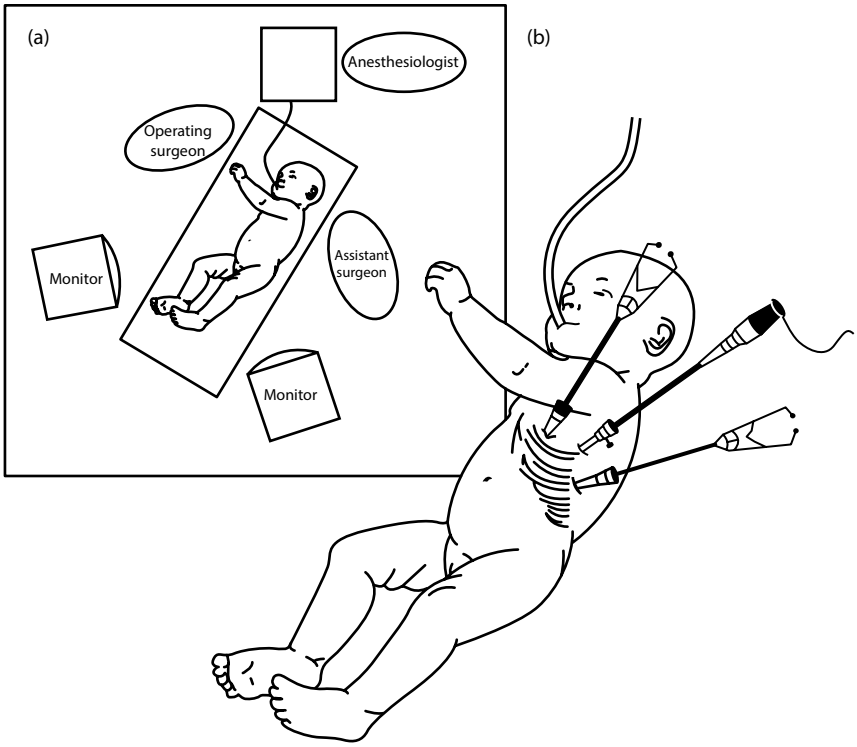

FIGURE 78.1 Drawing of patient positioning: (a) Trendelenburg and (b) side of interest up. You will need to adapt this drawing, but basically it shows patient positioning, with a child secured to the bed with straps across the knees and chest, and an image in the Trendelenburg and bed rotated positions to have the affected side up.

two 3 mm laparoscopic instruments to achieve triangulation on the inguinal ring of interest; however, it is worth mentioning that in the setting of bilateral hernias, the ports may be best placed in both the right and left lower quadrants in the midclavicular line to allow the surgeon to approach both sides (Figure 78.2).

At this point, whether a single-incision laparoscopic platform or a multisite setup is employed, the approach is similar. Any intraperitoneal contents or herniated bowel is reduced, and the patent inguinal ring is evaluated. Various approaches call for some combination of the following: (1) full dissection of the PPV, (2) simple interruption of the continuity of the peritoneum at the level of the inguinal ring, and (3) suturing closed the peritoneal surface of the intra-abdominal inguinal ring. Some surgeons may even include the conjoint tendon in the repair in an attempt to tighten the canal itself. Regardless, it is vital to assess the surrounding anatomy and, in boys, take care to not injure the spermatic vessels and the vas deferens. We prefer to use 3 mm instruments (an atraumatic grasper and scissors) to then interrupt the peritoneum diving into the PPV, which is done using a combination of cold-cutting and electrocautery. We then use a standard laparoscopic needle driver and absorbable suture to close the inguinal ring with interrupted sutures, again taking great care not to injure the vas (Figure 78.3, Video 78.2). While we prefer to interrupt the peritoneum directly by incising it prior to suture closure, some authors simply close the ring with nonabsorbable suture without any associated dissection.

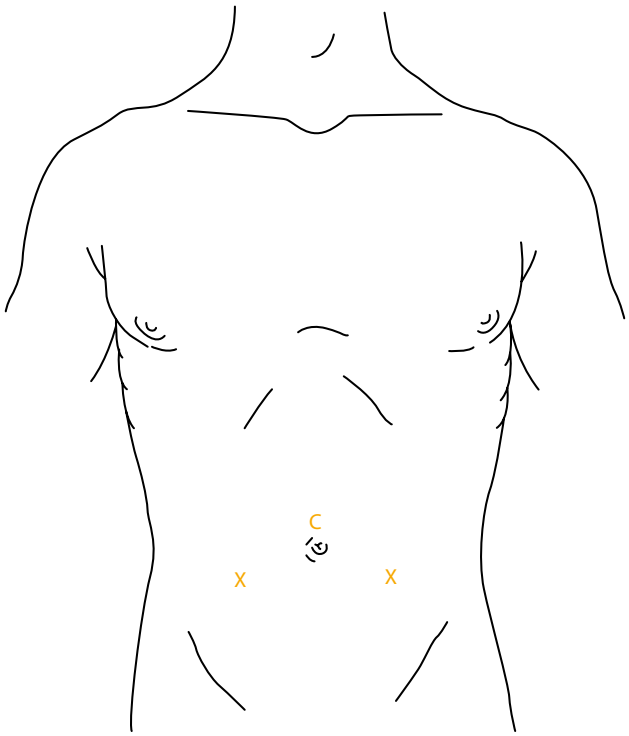

FIGURE 78.2 Schematic of port or instrument placement for standard laparoscopic inguinal hernia repair. C, 5 mm laparoscope; X, stab incisions for 3 mm instruments.

Transperitoneal Access and Endoscopic Visualization for Extracorporeal Management of the Inguinal Hernia

In general, this approach to manage inguinal hernias in children was initially developed in 1995 by Takehara and associates.[6] They termed this repair laparoscopic percutaneous extraperitoneal closure (LPEC). They described placing a laparoscope through an umbilical incision, inserting a 2 mm grasping forceps through a trocar on the left side of the umbilicus, and inserting a specially designed 19-gauge needle with suture material at the midpoint of the affected inguinal line. The opened hernia sac was closed extraperitoneally by circuit suturing around the internal inguinal ring using the LPEC needle.

Two novel variations on this theme described in the mid-2000s include the techniques of one-trocar laparoscopic-assisted extracorporeal closure: SEAL and PIRS (Figures 78.4 and 78.5).[7,8] In general, using intracorporeal laparoscopic visualization, the hernia defect is enclosed by a nonabsorbable suture, which is introduced into the abdomen by a needle on one side of the hernia defect, tracking under the patent processes and above the vessels and vas, and then withdrawn on the opposite side. Extracorporeal knot tying is subsequently performed. As a modification of single-port endoscopic-assisted ligation, in 2008 Bharathi et al. described "preperitoneal hydrodissection," with a small amount of saline injected using a hypodermic or spinal needle in the extraperitoneal space to lift up the peritoneum of the vas and the vessels. The suture could then be advanced to encircle the posterior hemicircumference of the defect.[9]

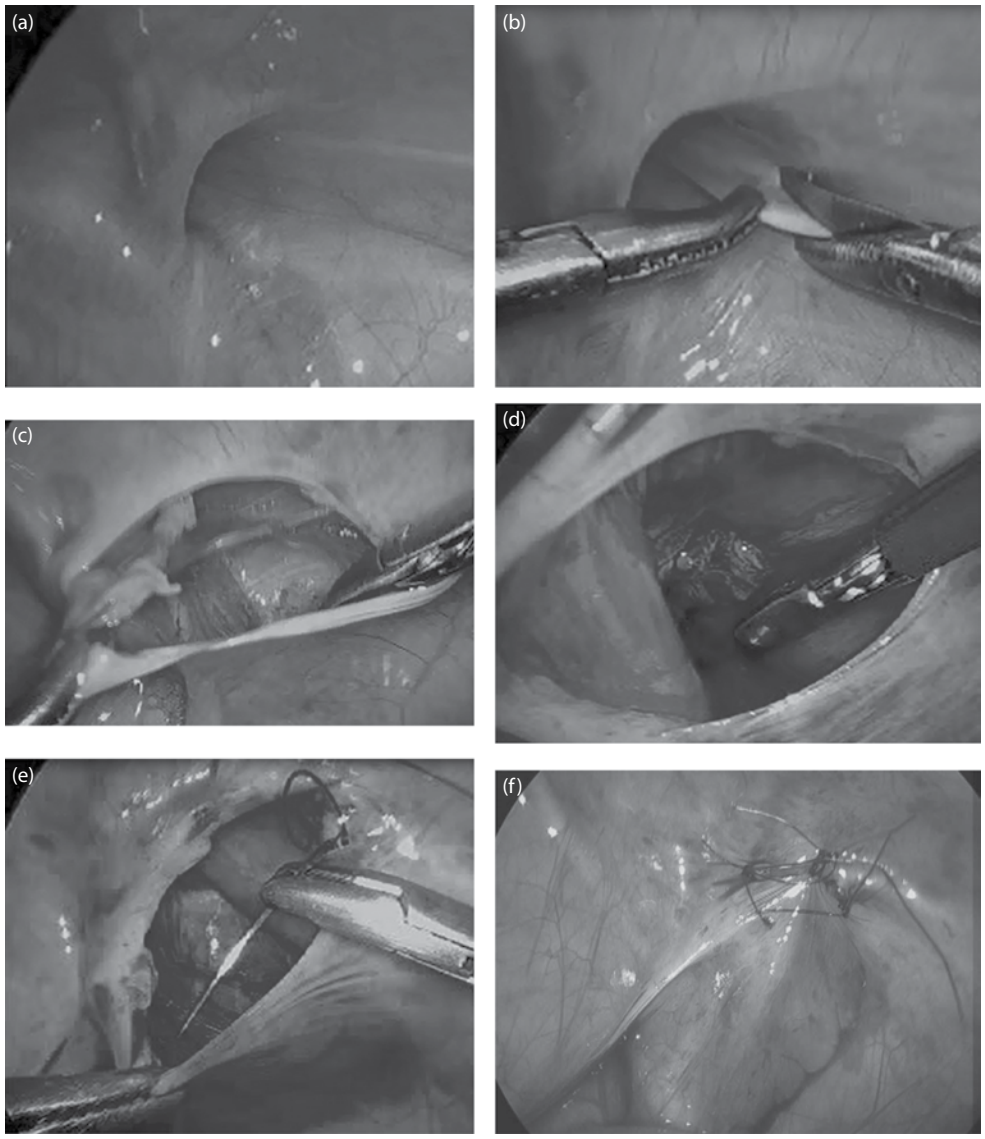

FIGURE 78.3 Standard transperitoneal laparoscopic inguinal hernia repair. Pictures: (a) Open right inguinal ring, (b) incising the peritoneum around the inguinal ring, (c) raising the peritoneum over the vas deferens and gonadal vessels, (d) peritoneal lining disrupted and distal sac retracted, (e) suturing the peritoneum closed, and (f) peritoneum closed with three interrupted, nonabsorbable sutures.

Despite the previously mentioned variations, the basic approach is the same, which involves transperitoneal access, followed by extraperitoneal suture closure of the PPV. Patient positioning is the same as demonstrated in Figure 78.1. After access is obtained, we prefer to use a 5 mm laparoscopic camera to visualize the inguinal ring of interest, as well as the contralateral inguinal ring. Any herniated contents can be reduced under direct inspection and may require placement of an additional instrument if they are incarcerated. Next, we use a hemostat on the skin while directly visualizing the ring intracorporeally to determine the best place to pass the needle from the outside. Preperitoneal hydrodissection can

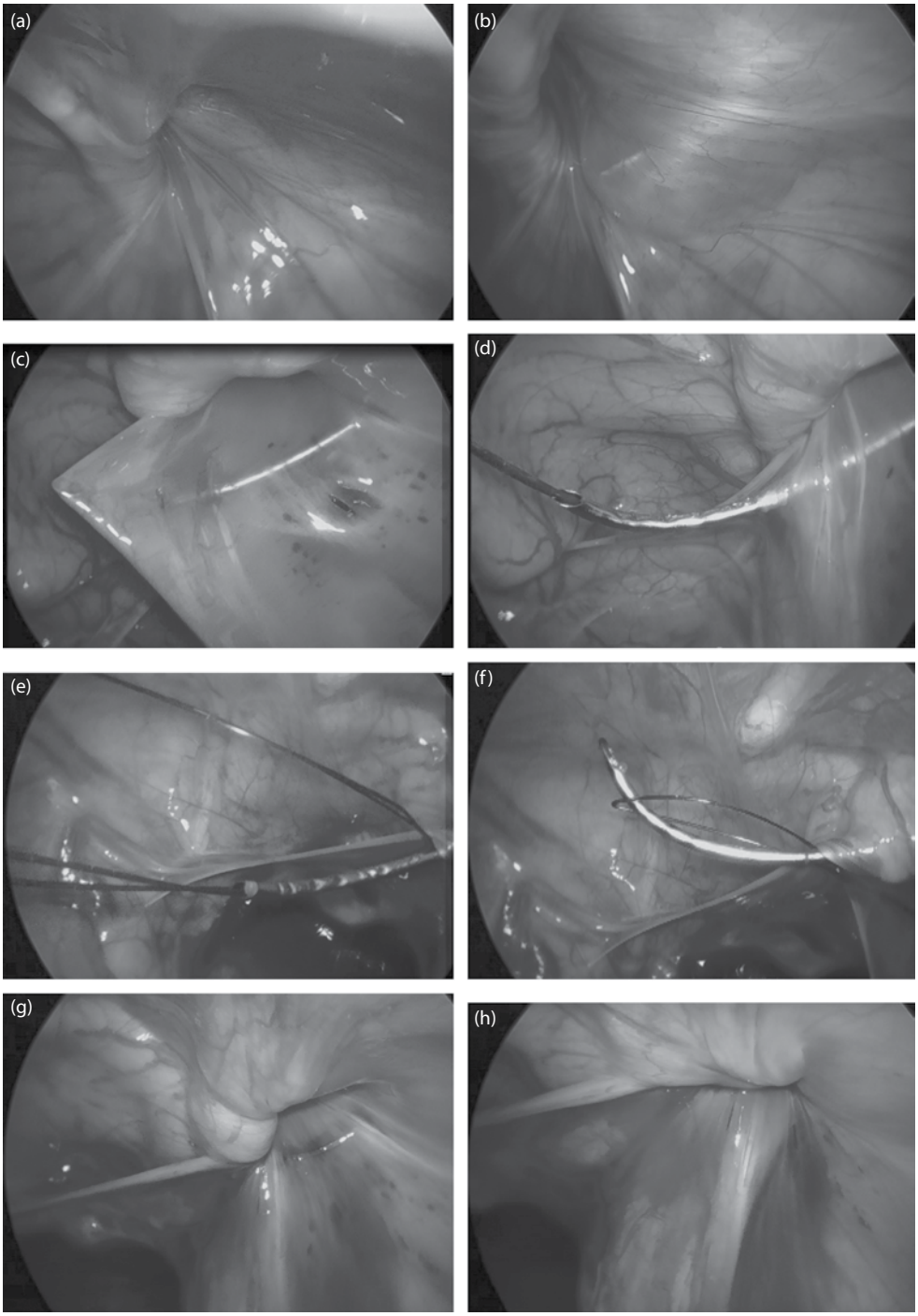

FIGURE 78.4 Pictures and video (Video 78.3) from a one-trocar laparoscopic-assisted extracorporeal hernia closure. Pictures: (a) open right inguinal ring; (b) hydrodissection of peritoneum off the vas and vessels (see needle coming in from laterally); (c) hollow needle being advanced under the ring, below the peritoneum and above the vas and vessels; (d) passing looped permanent suture through the hollow needle; (e) hollow needle advanced over the ring and exiting the peritoneum via the same peritoneal opening made from below—note the second looped permanent suture passed via the hollow needle; (f) loop suture placed around the second suture and pulled back around the bottom of the ring; (g) suture passed completely around the ring; (h) closed ring after suture tied down.

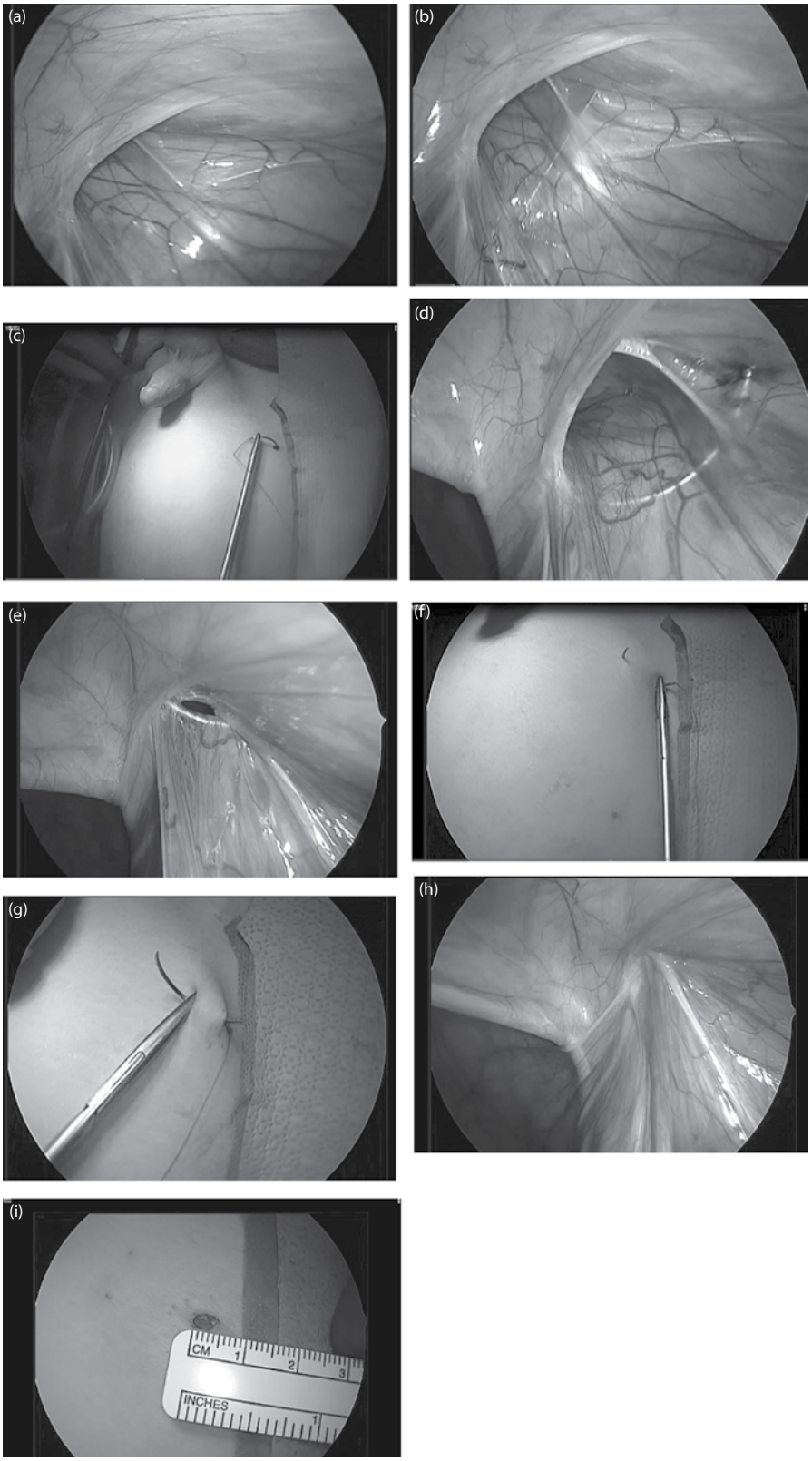

FIGURE 78.5 Pictures and video from an extracorporeal percutaneous minimally invasive inguinal hernia repair. Pictures: (a) Open right inguinal ring; (b) hydrodissection of peritoneum off the vas and vessels (see needle coming in from laterally); (c) CT needle with permanent suture being introduced extracorporeally; (d) CT needle being advanced under the peritoneum through the hydrodissection plane; (e) needle passed above the vas and vessels, under the peritoneum and encircling the PPV; (f) needle exiting extracorporeally; (g) needle being "back-loaded" through the original stab incision; (h) peritoneum closed once knot tied down extracorporeally; and (i) appearance of the stab incision prior to closing. (Pictures and video courtesy of Patrico C. Gargollo, MD, University of Texas Southwestern Medical Center, Dallas.)

be employed at this juncture, prior to passing the suture, to create a "potential space" above the vessels or vas and below the peritoneum. At this point, a small stab incision is made in the skin and subcutaneous tissue. Next, using a nonabsorbable suture on a computed tomography (CT) needle in a standard needle driver, from extracorporeally we gently advance the needle under the peritoneum but over the vessels or vas until the other side of the PPV is reached. The needle is then driven up through the skin until half of the needle is exposed; the back end of the needle can then be driven through the original stab incision. The suture is tied down encircling the PPV, all while visualized from internally to confirm secure closure (Figure 78.5). Of note, based on surgeon's preference, comfort, and the side he or she is operating on, one can start with the stab incision either medially or laterally relative to the affected inguinal ring.

PATIENT SELECTION AND INDICATIONS FOR PEDIATRIC INGUINAL HERNIA REPAIR

Surgery is indicated for all children once an inguinal hernia has been diagnosed. Premature infants or those under 3 months of age with an inguinal hernia are usually scheduled on a semiurgent basis. This is as opposed to the asymptomatic older child, who may be scheduled for surgery in a truly elective manner. In the setting of a communicating hydrocele, most surgeons will observe the majority of children less than 12 months of age,[10] and some children may continue to be observed for longer, as the majority of PPVs will close within the first 12–24 months of life.[10–12]

There is no place in children for conservative management of inguinal hernia. Operative indication is often delayed, although this is usually age dependent.[10,13] Surgery is offered for a communicating hydrocele after the age of 12 months because of persistent enlargement and the potential risk of hernia later in life, and to prevent future symptoms and avoid complicating the diagnosis of an acute scrotum in the future. Surgical treatment is offered for hernia to prevent the risk of incarceration, obstruction, and the necrosis of hernia contents, as well as surrounding cord structures. In females, torsion of the ovary is also possible.[10,14,15] There are no absolute or relative contraindications to inguinal hernia or hydrocele repair; however, surgery is often delayed for other reasons, such as fitness for surgery or issues of abdominal pressure, as occurs in reduction of large abdominal wall defects.

COMPLICATIONS OF MINIMALLY INVASIVE SURGERY FOR PEDIATRIC INGUINAL HERNIA

When discussing the specific complications of laparoscopic pediatric inguinal hernia repair, one must begin with complications secondary to the laparoscopic access in general. Laparoscopy carries its own set of complications, such as air embolism, hypothermia, decreased venous return, hypercapnia, acidosis, needle or trocar injury, and viscous or vessel injury. These are generally seen as a consequence of a lack of surgeon experience. In general, the insufflation pressure should be kept below 15 mmHg, especially in infants, to avoid respiratory compromise or hypercapnia. End-tidal carbon dioxide monitoring and core body temperature should be monitored rigorously in all babies. In addition, laparoscopic surgery carries risks of injury to the iliac vessels, the inferior epigastric vessels, and the gonadal vessels. In gaining laparoscopic access, there is a risk of vascular injury, and thus even these initial steps must not be taken lightly.[16,17] In the case of vascular injury, we stress the importance of adherence to surgical principles, starting with calmly directing the operative and anesthesia teams while gaining proximal and distal control of any bleeding vessel and avoiding reckless movements and potential further damage to surrounding structures.

Other risks of laparoscopic hernia repair are ones shared by open herniorrhaphy as well. Postoperative hydrocele deserves specific mention given the variation in the management of the distal sac in a laparoscopic repair. In some repairs, the distal sac is left intact, and thus raises concern for a higher rate of postoperative hydrocele. However, this has not been borne out when critically appraising the available literature. Similarly, recurrence is of special concern in laparoscopic repairs; the potential for incomplete closure of the ring circumference, the inclusion of tissues other than peritoneum in the ligature, and the failure to detect a direct hernia are some factors suspected as causes for recurrence.[18,19] Some authors have observed that boys have a higher recurrence rate than girls. During relaparoscopy, they found that most recurrences occur medially. Thus, the stitches at the medial aspect of the hernia, close to the vas, seem to be the most crucial ones.[18] This can explain the extreme caution and margin that a surgeon exercises while passing the needle close to the vas or epigastric vessels at the medial side of the internal ring. It seems that even leaving a small medial gap is enough to invite subsequent widening and hernia recurrence. It may be that these are more appropriately termed "incomplete closures" rather than true "recurrences." In girls, the surgeon will have no concerns in placing stitches medially. Therefore, this is probably the reason why girls have fewer recurrences.[18]

The other known complications with open surgery, such as iatrogenic tethering of the testis resulting in a secondary or acquired "undescended testis," chronic inguinal pain, and wound infections, are rare with the laparoscopic approach. Data regarding testicular atrophy and injuries to the vas are not yet available, as long-term results have not been studied. However, it has been proposed that these may be observed much less frequently in minimally invasive approaches, supposedly due to less and more precise dissection enabled by magnification.[16]

OUTCOMES

Laparoscopic repair has been increasingly employed over the last two decades for pediatric inguinal hernias; however, in terms of outcomes, it will always be compared with the long-standing results from open herniorraphy. Proponents of the minimally invasive approach cite the ease of examining the contralateral internal

ring, decreased manipulation of the vas deferens and spermatic vessels, decreased operative time, and an ability to identify unsuspected direct or femoral hernias. The only level 1 evidence in support of a comparison between open and laparoscopic pediatric inguinal hernia repair is a prospective single-center, randomized study of 97 patients from 2005.[20] In their experience, while the operative time for laparoscopic approach took approximately 5 min longer, it was associated with statistically significantly decreased pain, improved parental perception of faster recovery, and a parental perception of better wound cosmesis. The laparoscopic approach also allowed for detection of contralateral hernia at the same time, and this was associated with a statistically significantly lower rate of detecting metachronous contralateral hernias during follow-up. However, various authors have reported varying experiences in terms of success and complications (Table 78.1).

There is clearly an element of experience and the presence of a learning curve that impact the time necessary to complete any operative procedure, as well as the rates of success and complications. In this regard, laparoscopic pediatric inguinal hernia repair is no different, and analyses have shown that increased experience leads to shorter operative time and improved outcomes.[19,25,33,34] One study investigated a learning curve of 75 cases, demonstrating a reduced recurrence rate after that mark.[34] A recent meta-analysis compared series in the literature of open and laparoscopic pediatric hernia repairs with similar findings as the previously mentioned randomized trial.[33] The average reported operative time for a unilateral laparoscopic herniorrhaphy ranges from 10 to 55 min.[16,25,33] This compares to open unilateral herniorrhaphy at 18–52 min, which was not statistically significantly different.[33] However, in the setting of bilateral hernia repair, the laparoscopic approach was statistically significantly shorter, with a range of time reported from 34 to 70 min compared with open repair at 39–95 min.[33] Similarly, the laparoscopic approach showed a statistically significantly reduced rate of metachronous contralateral hernia, with an odds ratio of 0.26. The actual rates of metachronous contralateral hernia varied for open repair from 3% to 11% and for laparoscopic repair from 0% to 6%. Also, in this meta-analysis no significant difference was observed between laparoscopic and open repair in duration of hospital stay, time to resume full activity, recurrence, and complications.

Specifically on the topic of recurrence and complications, there are a variety of reports in the literature, and as previously mentioned, experience clearly plays a role in these outcomes.[25,33,34] The reported rate of recurrence for open herniorrhaphy is between 0% and 5%, which is similar to that in most reports of laparoscopic pediatric inguinal hernia repair, with the exception of one outlying study reporting a recurrence rate of 27%.[26] Factors thought to portend lower recurrence rates include female sex,[18] young patient age,[34] and surgeon volume and experience.[11,12,14]

As previously mentioned, there are risks from hernia repair, both open and laparoscopic. While some authors

TABLE 78.1 Published outcomes of minimally invasive pediatric inguinal hernia repairs

Study (first author)	Technique (traditional lap vs. percutaneous)	Operative time in minutes (unilateral/bilateral)	Intraop complications (%)	Recurrence (%)	Hydrocele (%)	Testicular atrophy (%)
El-Gohary[2]	Traditional	12–15/15–20	0	0.03	—	—
Zallen[21]	Traditional	—	0	0	—	—
Schier (2002)[19]	Traditional	16/23	—	3.4	0.6	0.2
Schier (2006)[18]	Traditional	10–55	0	3.7	0.7	0.2
Gorsler[22]	Traditional	14/21	0.004	2.7	1.7	0.004
Chan[20]	Traditional	23/34	0	1	0.02	—
Chinnaswamy[23]	Traditional	21–35/28–50	0	3.1	0.03	0
Saranga Bharathi[16]	Traditional	25/46	1.5	3	3	1.5
Becmeur[24]	Traditional	23–28/30–40	0	0	0	0
Yip[25]	Traditional	26/38	0	0	3.1	0
Hassan[26]	Traditional	40–55	27	27	0	0
Koivusalo[27]	Traditional	15–59	0	4.3	—	0
Tsai[28]	Traditional	52/70	0	1.1	0	—
Shalaby[29]	Percutaneous	8.7/12.4	0	0	0	0
Spurbeck[30]	Percutaneous	38/47	0	0.83	0	0
Oue[31]	Percutaneous	45/54	0	0	—	—
Takehara[6]	Percutaneous	15/30	0	0.73	0	0
Patkowski[8]	Percutaneous	19/24	0.04	0.03	0.05	—
Endo[32]	Percutaneous	28/36	0	0.2	—	0

describe a lower complication rate with one or the other approach, most reports find no difference between the two. Reported rates for any complication (including recurrence) vary between 1% and 27% for laparoscopy and between 0% and 16% for open repairs. Specific complications, such as postoperative hydrocele, are a concern because in a laparoscopic herniorrhaphy, the distal portion of the sac is left intact without even being split. However, the rates are surprisingly low (0%–5%), which compare favorably to those of open repairs (0%–3%). Other known complications with open surgery, such as iatrogenic tethering of the testis, inguinodynia, and wound infections, are almost unseen in laparoscopic repairs. Testicular atrophy and injuries to the vas are rare complications even in open herniotomy and seem to be observed even less frequently in laparoscopic repairs.[16]

One additional area of concern is the added cost of laparoscopy in this setting. While a full cost-effectiveness analysis has yet to be done, a recent limited analysis indicated that open repair after reduction of an incarcerated hernia was more cost-effective than laparoscopy.[27] This is despite findings similar to those above with decreased hospital stay for laparoscopic repair. The increased cost was mostly carried by the fixed cost of the instrumentation and equipment, in addition to increased operative time. However, this was a limited analysis, only factoring in the cost of surgery and hospitalization; it did not account for other factors, such the need for a later contralateral repair, the cost of repeat visits and hospitalization for recurrence, and the societal cost of missed parental work related to longer hospital stay. It is worth noting that diagnostic laparoscopy alone, when looking for a contralateral inguinal hernia at the time of open hernia repair, has been demonstrated as cost-effective.[35]

Given the relatively new development of the various novel laparoscopic techniques (i.e., LPEC, SEAL, and PIRS), there are a lack of long-term data to allow proper comparison to traditional laparoscopic or open pediatric inguinal hernia repair. However, the results to date for recurrence and/or complications appear to reflect the overall experience with traditional laparoscopic repair.[16,36,37] While these various numbers may provide a broad overview of the general experience with laparoscopic inguinal hernia repair in children, the guiding mantra for a surgeon should be to perform the procedure that in your hands provides the best and safest outcomes and use your personal data for patient counseling.

SPECIAL CONSIDERATIONS

Management of the Contralateral Inguinal Ring

There could easily be textbook chapters written solely on the topic of managing a contralateral PPV when detected laparoscopically. This is because of the known risk of metachronous contralateral inguinal hernia when performing a unilateral hernia repair. Obviously, detection of this contralateral PPV laparoscopically would allow for simultaneous closure; however, there is debate about the natural history of such a PPV. Data from a series of laparoscopic exploration demonstrate a rate of contralateral patency between 10% and 40%.[16] However, a recent, large retrospective review on the issue found that when not addressing an asymptomatic contralateral PPV, the rate of metachronous hernia is approximately 2%. This compares with a recurrence rate of 0.2% if the contralateral PPV is repaired at the same time.[38]

While such limited data would support the routine inspection and repair of contralateral patency, the debate is far from settled. The questions surrounding the issue are as follows: (1) What percentage of these contralateral PPVs truly become symptomatic? (2) Does detection of all contralateral PPVs lead to overtreatment? (3) Is it effective to detect and treat all contralateral PPVs in order to avoid a second anesthetic in the group that eventually develop a true inguinal hernia? (4) Are there ways to determine which patients should have inspection for and/or treatment of a contralateral PPV?

Management of Bilateral Inguinal Hernias

As mentioned earlier in the text, the current data would seem to support the role of minimally invasive approaches to bilateral hernias and communicating hydroceles. There are multiple reports on the fact that with one approach, it is possible to repair both sides, and typically this can be done more quickly than with bilateral open inguinal approaches.[33] Clearly, there are the same risks that exist when approaching a single inguinal ring, such as potential injuries from obtaining peritoneal access, potential vasal or vessel injuries, and risks of recurrence. However, given the defined decrease in operative time, minimally invasive approaches are a reasonable alternative in the setting of bilateral pediatric inguinal hernias.[33]

Management of Recurrent Inguinal Hernias

For recurrent hernias after previous open hernia repair, reoperation with an inguinal incision requires going through the old operation site, which in boys almost always has the vas deferens and testicular vessels embedded in dense fibrous tissue. The operation is tedious and risks damaging these important structures. In such a scenario, laparoscopy allows approaching the pathology from the virgin area and helps avoid the previous operation site. So in effect, technically it may be as simple as a fresh laparoscopic hernia repair. Also, laparoscopy accurately identifies the nature of the defect in children with recurrent groin hernias, detecting unsuspected contralateral indirect, direct, or femoral hernias in a large number of those undergoing laparoscopy.[39]

Management of Incarcerated Inguinal Hernia

The issue of manual reduction of the bowel while the patient is under anesthesia is still controversial; however, using the laparoscopic approach solves this controversy, for the bowel is examined in the peritoneal cavity without the need to manipulate outside through the internal ring,

as happens with the open technique. It is reported that creation of the pneumoperitoneum itself dilates the ring sufficiently, aiding in the reduction of the incarcerated contents. In addition, external compression, forbidden in conventional surgery, is found to be safe and useful because the contents can be observed from inside. Even gentle traction with endoscopic instruments is safe under vision and can facilitate reduction of hernia contents immensely.[40] Laparoscopy also aids in allowing for intracorporeal assessment of the viability of the incarcerated intestine, and if the contents prove unviable, as a result of strangulation, they can be excised totally laparoscopically[41,42] or be laparoscopically guided by a mini-laparotomy on top of the area where the nonviable contents have been laparoscopically placed.[43] One advantage of laparoscopy for incarcerated hernias is that laparoscopic herniorrhaphy is usually done from within the abdomen and bypasses the edematous surrounding tissue and spermatic cord structures, and thus the repair is performed in nonedematous tissue at the internal ring.[44]

Management of Female Inguinal Hernias and Potential for Abnormalities of Mullerian Structures

A minimally invasive approach to female patients with presumed inguinal hernias is ideal because it allows for the assessment of Mullerian structures at the same time as the inspection of the peritoneal cavity to assess the affected inguinal ring. In the setting of open inguinal hernia repair for female patients, the surgeon must confirm the presence of Mullerian structures either via inspection of the peritoneal cavity by pulling on the round ligament to observe a fallopian tube or by concurrent assessment of vaginal length or vaginoscopy.[45,46] However, in utilizing laparoscopic visualization, the surgeon can assess for the presence of Mullerian structures and investigate the potential for complete androgen insensitivity syndrome (CAIS). While only a small minority of prepubertal females with an inguinal hernia will have CAIS (1%–2%), up to 75% of patients with CAIS will present in this manner.[47,48] Thus, it is a diagnosis that must be excluded, and the use of laparoscopic access can prevent the need for ancillary procedures. An additional benefit is the ability to assess the gonads in the setting of CAIS. While it is not determined what the role is for gonadectomy at the time of diagnosis, as opposed to postpubertally, the laparoscopic access does allow for gonadectomy at the same setting, depending on the wishes of the family, as well as the team of surgeons, endocrinologists, geneticists, pediatricians, and psychologists.[46]

Similarly, the entity of hernia uterae inguinale is uncommonly encountered in phenotypically normal boys in the setting of a Mullerian inhibiting substance (MIS) deficiency and persistent Mullerian duct syndrome. While the discovery of Mullerian structures during an inguinal hernia repair can be confusing to the surgeon, as well as the family, a minimally invasive approach offers many advantages, as outlined by a recently published algorithm in managing these patients.[49] In addition to allowing for repair of the hernia, laparoscopy allows for both visualization and biopsy of the gonads and potentially even intra-abdominal reconstruction and orchiopexy or gonadectomy.[50]

CONCLUSIONS

Pediatric inguinal hernias can be safely and reliably managed by a minimally invasive approach, in both males and females, in a wide range of clinical scenarios, from a communicating hydrocele, to a true hernia, to a contralateral PPV, and even for an incarcerated hernia. There are many techniques and variations on the minimally invasive approach to pediatric inguinal hernia repair, and at this point, all seem to have similar efficacy and safety profiles. The most important factor for outcome appears to be surgeon experience. However, while we lack level 1 data demonstrating superiority or equivalence to traditional open inguinal herniorrhaphy, the current data indicate that it is a reasonable and safe alternative to offer patients and their families.

MULTIMEDIA FILES AVAILABLE ONLINE (www.crcpress.com/cw/Docimo)

VIDEO 78.1 Transperitoneal laparoscopic inguinal hernia repair in a female infant.

VIDEO 78.2 Standard transperitoneal laparoscopic inguinal hernia repair.

VIDEO 78.3 One-trocar laparoscopic-assisted extracorporeal hernia closure.

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CHAPTER 79

Cryptorchidism

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INTRODUCTION

Cryptorchidism or undescended testes (UDT) are the most common disorder of the male endocrine glands in children. One-third of boys with true cryptorchidism have bilaterally cryptorchid testes, while two-thirds are *unilateral*.[1] The main reasons advocated for treatment of cryptorchidism are impaired fertility, increased risk of testis cancer, increased risk of developing testicular torsion, injury against the pubic bone, and the psychological stigma of an empty scrotum.[2–4] The current standard of therapy in the United States has been the surgical repositioning of the testis within the scrotal sac (orchidopexy), while hormonal manipulation has been more widely used in Europe. However, despite successful relocation of the testis, long-term sequelae of cryptorchidism occur, including infertility, subfertility, and malignancy.

EPIDEMIOLOGY

Cryptorchidism is a common developmental abnormality with a prevalence of 1%–3% in full-term and 15%–30% in premature male infants. In age-corrected full-term boys, spontaneous descent may occur in the first 6 months of life.[5,6] Accordingly, the prevalence decreases to about 0.8% in previously full-term infants at 1 year of age and remains there essentially throughout adulthood. Two-thirds of persistent UDT are unilateral and one-third are bilateral.[1] In boys with unilateral UDT, the right testis is affected twice as often as the left.

In the last decade, the phenomenon of ascending testes (acquired cryptorchidism), which are previously descended testes that ascend out of and cannot be manipulated into the scrotum, has been recognized. An increase in UDT was reported in the United States and South America during the 1970s and 1980s, but since 1985, rates have stabilized or declined in most countries.[7–9] Variability in cryptorchidism rates may be due to observer error with retractile testes, testicular ascent, or previously unrecognized UDT in the high scrotal or superficial inguinal pouch regions.

A number of obstetrical risk factors have been suggested as possible risk factors for UDT, including advanced maternal age, maternal obesity, breech presentation, cesarean section, low parity, consumption of cola-containing drinks during pregnancy, preterm birth, and low birth weight.[6,10–13] Further, hypospadias and a family history of cryptorchidism have also been associated with UDT.[14–16] The incidence of UDT is also directly related to the position of the meatus in boys with hypospadias. Up to 30% of infants with proximal hypospadias will exhibit concomitant cryptorchidism compared with only 2.5%–5% for distal hypospadias. Birth weight has also been closely associated with cryptorchidism: infants of <900 g have approximately 100% incidence of UDT. This incidence steadily decreases as the birth weight of the infant increases (to 3.3% for 2700–3600 g infants).[17,18]

Ascending Testes

Acquired cryptorchidism (or ascending testis) is the ascent of a previously descended testis and subsequent inability to manipulate the testis back into the scrotum. Ascended testes are at risk for developing the same adverse histologic changes seen in primary cryptorchid testes and contribute significantly to the number of orchiopexies performed.[19–26] Acquired cryptorchidism has a reported prevalence of 1%–7% and peaks around 8 years of age.[27–29] Aberrant androgen signaling has been associated with ascending testes. This is supported by the report that boys with a history of proximal hypospadias are at increased risk of developing ascending testes.[30] Given that retractile testes are at risk of becoming true ascended testes, yearly examination of boys with retractile testes or a history of proximal hypospadias is recommended, which could be performed by the pediatrician or pediatric urologist.[31–34]

"Trapped" Testes

In patients who have undergone previous inguinal or scrotal surgery, the testis can become trapped in scar tissue above the dependent scrotum. Identification of the testis can be quite difficult in children who have previously had inguinal or scrotal surgery. Due to the scarring, there is limited mobility of the spermatic cord and, accordingly, increased risk of injury to the testis during operative repair. Various approaches include en bloc mobilization of the spermatic cord and use of a scrotal approach.[35,36]

GONADAL DEVELOPMENT

Proliferation and migration of primordial germ cells from the yolk sac into the mesonephric bodies begins in the

fourth gestational week. By the sixth week, the primordial cell migration from the wall of the embryonic yolk sac along the dorsal mesentery of the hindgut to the genital ridge is completed.[37] These processes accelerate during weeks 5–6, forming the bipotential gonad that replaces the regressing mesonephric body by the end of the sixth week. Differentiation of the bipotential gonad into the testis occurs under control of the SRY (sex-related gene on Y chromosome) gene. Development of testicular histology and endocrine function begins during the seventh gestational week and continues into adulthood. Testis maturation is characterized by four steps (two prenatal and two postnatal) prior to the final maturational changes at puberty.

First, primordial germ cells enter the emerging testicular cords and differentiate into gonocytes. These gonocytes constitute the fetal stem cell pool of the germ cell line and lie in the center of the testicular cords. Human chorionic gonadotropin (hCG) stimulates fetal Leydig cell development, proliferation, and testosterone secretion. Gonocyte proliferation expands the fetal stem cell pool, while fetal Sertoli cells simultaneously differentiate and begin to secrete Müllerian inhibiting substance (MIS). Masculinization of the mesonephric (Wolffian) duct, paramesonephric (Müllerian) duct, and external genitalia begins. MIS causes regression of Müllerian structures, and testosterone causes development of the Wolffian duct, to form the epididymis and vas deferens.[38,39]

In the second step in maturation, gonocytes begin to migrate to the basement membranes of the seminiferous tubules and differentiate into fetal spermatogonia. In this phase, the level of hCG, number of fetal Leydig cells, and level of testosterone reach their peaks during the 13th week of gestation. Masculinization of the external genitalia and resorption of the paramesonephric ducts is completed. Masculinization of the mesonephric duct into the epididymis continues, and the swelling of the gubernaculums begins. Differentiation of fetal spermatogonia continues throughout fetal life. Canalization of the rete testis and mesonephric tubules begins in week 12 and is completed by puberty. Testicular descent occurs in the seventh month of gestation and depends on the multiple factors discussed earlier.

The third step occurs postnatally during the second month after birth (Figure 79.1). By now, the seminiferous tubules contain numerous germ cells. Approximately half are gonocytes, and the rest are fetal spermatogonia. A surge in luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels stimulates proliferation of fetal Leydig cells, in turn causing a surge in testosterone. A minority of gonocytes attach to the tubule basement membrane and differentiate into adult dark (Ad) spermatogonia, while the majority undergo apoptosis, thus lowering the total germ cell number. Consequently, the gonocyte fetal stem cell pool is replaced by Ad spermatogonia, which ultimately comprise the stem cell pool in adults. The transformation and disappearance of gonocytes is normally completed by 6 months of age. The levels of gonadotropins and testosterone fall as fetal Leydig cells become juvenile Leydig cells, which are quiescent. Some Ad spermatogonia mature into adult pale (Ap) spermatogonia. Fetal Sertoli cells mature into Sa Sertoli cells.

At approximately 5 years of age, the fourth important maturational step commences with the onset of meiosis. Simultaneous transient peaks of LH, number and size of juvenile Leydig cells, and testosterone occur. The increased testosterone stimulates an increase in Ad spermatogonia and the total germ cells. It also triggers the maturation of the mitotic Ad spermatogonia into primary spermatocytes, which are germ cells in the prophase of the first meiotic division. Sa Sertoli cells mature into Sb Sertoli cells.

Final germ cell maturation at puberty depends on adequate completion of the two prepubertal developmental milestones. The pubertal surge in LH and FSH stimulates the inactive juvenile Leydig cells to multiply and mature into adult Leydig cells. These adult Leydig cells produce the high pubertal surge in testosterone, which triggers the final maturation to secondary spermatocytes, early and late spermatids, and sperm. Sertoli cells undergo their final maturation into Sc Sertoli cells. Complete spermatogenesis is usually accomplished by 13–15 years of age.

In the cryptorchid testis, the number of Leydig cells is decreased and they appear atrophic (Figure 79.2). In the first 6 months of life, the total number of germ cells is within the normal range in cryptorchid testes; however, the number of spermatogonia remains low and does not

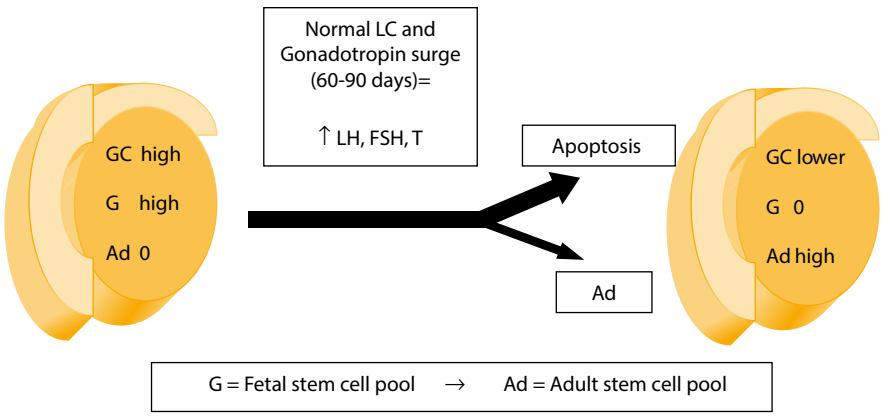

FIGURE 79.1 Third step in maturation: Differentiation of fetal gonocytes into Ad spermatogonia. GC = total germ cell count, G = gonocyte, Ad = adult dark spermatogonia, LC = Leydig cell, T = testosterone.

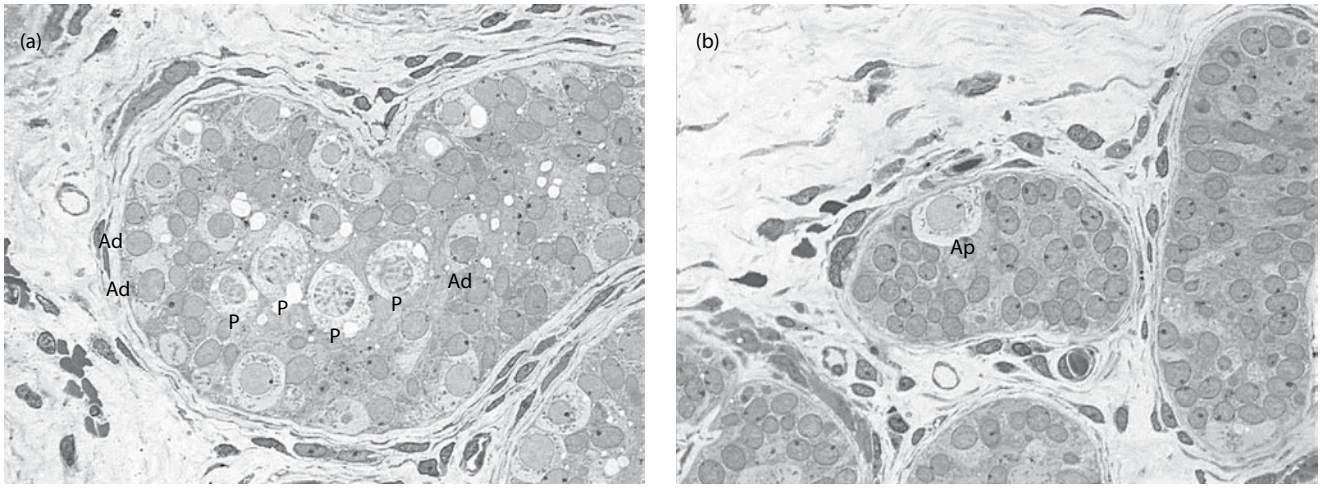

FIGURE 79.2 (a) Descended testis biopsy showing Ad spermatogonia and primary spermatocytes (P). (b) Cryptorchid testis biopsy showing paucity of Ad spermatogonia and persistence of fetal gonocytes with Ap spermatogonia.

increase with age. Histologic examination of cryptorchid testes has shown that testes that remain undescended are associated with progressive loss of germ and Leydig cells.[22] There are reports that gonocytes fail to transform into Ad spermatogonia in the cryptorchid testis.[40] The normal postnatal development of Leydig cells and germ cell transformation parallels the normal gonadotropin and resultant testosterone surge around 60–90 days of life.[41,42]

ETIOLOGY

Despite the relatively frequent incidence of cryptorchidism, the etiology and molecular markers of future fertility or malignancy remain obscure. Cryptorchidism is a well-known manifestation of chromosomal abnormalities and a common component of more than 50 syndromes of multiple congenital anomalies. Cryptorchidism, when associated with other congenital anomalies, like hypospadias, has a higher incidence of chromosomal anomalies (12%–25%) than when it occurs as an isolated defect (3%–4%).[43–45] However, at present, there is no consistent chromosomal disorder associated with isolated cryptorchidism.

Cryptorchidism can be viewed as an endocrinopathy. Cryptorchidism accompanies defects in every intrinsic step of the hypothalamic–pituitary–testicular–end organ axis, as well as defects in extrinsic pathways that affect the axis, such as extratesticular cholesterol synthesis, adrenal steroidogenesis, placental "insufficiency," and maternal or environmental endocrine disruptors. Huff clarified the central role of cryptorchidism in the endocrinopathy of hypogonadism. In his analysis of cryptorchid boys, more than 70% of those examined had one or more of these late defects of masculinization associated with the endocrinopathy of hypogonadism. He classified the multiple conditions upstream from cryptorchidism into errors of blastogenesis, organogenesis, sexual differentiation, and late masculinization; while the cascade of events downstream from cryptorchidism are testicular atrophy, microlithiasis, intrauterine torsion, Sertoli cell nodules, and most importantly, germ cell maldevelopment. The abnormal proliferation and maturation of germ cells in cryptorchidism leads to an overall decrease in total germ cell counts and loss of the adult stem cell population. These alterations in germ cell maturation and proliferation produce the most important tertiary abnormalities of the sequence: subfertility and testicular neoplasia.[46]

Several case series of the familial occurrence of cryptorchidism have demonstrated that a heritable component exists.[47,48] Furthermore, large epidemiologic studies have shown a consistent pattern of inheritance for isolated cryptorchidism. Of boys with UDT, 4.0% of their fathers and 6.2%–9.8% of their brothers also had UDT.[6] Elert et al. conducted a study to examine the frequency of a positive family history and to calculate the risk for the newborn male boys to have a UDT. They reported that boys born to parents with a family history of cryptorchidism have a 3.6 times higher odds of having cryptorchidism.[49] These inheritance patterns are consistent with a multifactorial etiology of cryptorchidism. Based on murine gene knockout models, some of the candidate genes involved in cryptorchidism are homeobox (*HOX*), calcitonin gene-related peptide (*CGRP*), insulin-like hormone (*INSL3*), G-protein-coupled receptor affecting testis descent (*LGR8* or *GREAT*), androgen receptor (*AR*), and the estrogen receptor 1 (*ESR1*) genes. In a large, well-designed, cohort study, 3.3% of boys with UDT that did not spontaneously descend had identifiable genetic alterations in the karyotype INSL3, AR, or relaxin family peptide 2 gene (RXFP2). This represented a 10 times greater odds of having a mutation in these genes than controls. The likelihood of having a genetic alteration was higher in those boys with bilateral cryptorchidism (OR 27.1).[50]

Androgen Influence

Hutson has proposed that testicular descent occurs in two phases. The initial transabdominal aspect may be controlled by MIS.[51] The inguinoscrotal descent appears to be androgen dependent and is mediated indirectly through the release of CGRP. Androgens act on the genitofemoral

nerve (GFN), which is sexually dimorphic and releases CGRP upon stimulation, producing rhythmic contractions of the murine gubernaculum. Hutson et al. found two rodent models of cryptorchidism to have deficiencies of CGRP in the GFN (the Tfm mouse and the rat prenatally exposed to antiandrogen).[52,53] Alternatively, Huff has proposed that there is only a transinguinal phase of testis descent based on a pathologic examination of human fetal specimens at Carnegie Human Embryos.[54] According to this theory, after gonadal formation, the formerly suggested "transabdominal migration" is actually a single position where the abdominal testis "appears to descend" due to the unfolding of the human embryo around 8–9 weeks of gestation, as it moves from the embryonic to the fetal stage of development.

Inguinoscrotal descent is blocked in mice with complete androgen resistance (testicular feminization) where the *AR* gene has been knocked out.[51,55] Deletions and mutations may cause structural changes in the AR, altering its function.[56] Up to 50%–70% of male pseudohermaphroditism, which includes hypospadias and cryptorchidism, is due to *AR* gene disorders (androgen insensitivity syndrome [AIS]), suggesting a role for androgens in this developmental process.[57,58] Other studies have shown that prenatal androgen disruption and androgen receptor polymorphisms are associated with hypospadias and primary cryptorchidism, which further supports the central role of androgens in testicular and penile development.[59–63] The majority of *AR* gene mutations identified are in the DNA-binding (exons 2–3) and ligand-binding (exons 5–8) domains. However, the same mutation can result in a different or even a normal phenotype in members of the same family.[64,65] It appears that phenotypic variations in families affected by partial AIS are modulated by factors other than or in addition to point mutations of the *AR* gene. Furthermore, the role of the *AR* gene mutations in isolated forms of hypospadias or cryptorchidism is an active area of investigation. It is a definite yet uncommon cause of hypospadias.[66–68] Since the last edition of this chapter, mutations in the androgen receptor have been identified in boys with isolated cryptorchidism.[50]

Exon 1 of the *AR* gene contains the transactivation domain and encodes polymorphic glutamine (cytosine–adenosine–guanine [CAG]) repetitive sequences. The CAG repeat length ranges from about 15 to 30 units in controls, exhibiting ethnic variability.[69] Within this spectrum, the CAG length influences androgen receptor function, providing enhanced androgen action with a shorter repeat length and decreased function with a longer length.[70] Mutations in a series of CAG trinucleotide repeat sequences located at a polymorphic region in exon 1 of the *AR* gene have been linked to an X-linked neuromuscular disease termed spinal bulbar muscular atrophy or Kennedy's disease.[71] These affected men display subtle signs of androgen resistance, such as gynecomastia, testicular atrophy, and reduced fertility. Increased AR CAG length has also been related to male infertility through defective spermatogenesis, although others have found conflicting results.[72–74] Within the normal polymorphic range, an expansion of the CAG tract decreases the androgen receptor activity and may be associated with cryptorchidism, infertility, and recently, testis cancer.[75–77] The association of CAG repeat lengths with these three conditions suggests that CAG length may have a central role in testiscular dysgenesis syndrome, which is composed of cryptorchidism, poor semen quality, hypospadias, and testicular cancer. Casella et al. have seen an increased CAG length when both cryptorchidism and hypospadias are present.[78] Ogata et al. reported an abnormally expanded CAG length in a boy with undermasculinized genitalia, but later concluded that CAG expansion is not likely a major cause of cryptorchidism.[79,80] Ferlin et al. analyzed CAG and GGC exon 1 repeat lengths in 105 formerly cryptorchid men compared with 115 fertile noncryptorchid men.[81] No difference was found when considered separately, but some combinations of repeat lengths are significantly more frequent in men with bilateral UDT, in a manner similar to that in findings in idiopathic infertile males.

Although historic studies have shown that androgen levels in adult men with a history of hypospadias do not differ from those of controls,[82] more recent studies have indicated that prenatal androgen disruption and androgen receptor polymorphisms are associated with hypospadias and primary cryptorchidism.[59–63] The theory is supported by the findings of Acerini et al., who reported that boys who developed acquired cryptorchidism had shorter penile lengths at 2 years than normal boys and boys with primary cryptorchidism, a difference that did not exist at birth.[29]

Estrogen Influence

The *ESR1* gene is a potentially important candidate gene for UDT. In a Japanese population, Yoshida et al. performed *ESR1* analysis in 63 cryptorchid boys and 47 controls by screening 30 single-nucleotide polymorphisms (SNPs) in the gene.[83] They found a significantly higher polymorphism frequency of an AGATA haplotype (SNP12) within the intron in cases than in controls (34% vs. 21%), and the association of the haplotype with UDT was significant in a recessive mode. The investigators speculate that this SNP enhances *ESR1* signaling. However, when these same SNPs were analyzed in a multiracial population, SNP12 was not associated with the occurrence of cryptorchidism, but was associated with the severity of cryptorchidism.[84] These results suggest that excessive estrogenic effects may decrease expression of INSL3 in Leydig cells, affecting the development of the gubernaculum, and so testicular descent. Further, excessive estrogenic signaling may suppress gonadotropin production and the steroidogenic capacity of Leydig cells, resulting in androgen deficiency.

Similar alterations in sex hormones have been hypothesized to increase the risk of hypospadias.[85,86] Although historic studies have shown that androgen levels in adult men with a history of hypospadias do not differ from those in controls,[82] more recent studies have indicated that prenatal androgen disruption and androgen receptor polymorphisms are associated with hypospadias and primary cryptorchidism.[59–63]

INSL3/RXFP2 Genes

Several investigators have examined the role of Leydig insulin-like hormone as a putative trophic hormone of

the first part of testicular descent. It is a member of the insulin hormone superfamily and is expressed in the developing testis. Mice mutant for *Insl3* are viable but exhibit bilateral cryptorchidism.[87–89] These mice have developmental abnormalities of the gubernaculum and abnormal spermatogenesis and infertility. However, in a manner similar to that of the *AR* gene, mutations of the *INSL3* gene in humans are infrequent.[90–92] RXFP2 (also known as GREAT and LGR8), which is the receptor for INSL3, is also highly expressed in the gubernaculum.[93–95] Mutations in this gene have been associated with cryptorchidism in the mouse and rarely in the human.[96–98] Screening of approximately 700 patients with UDT for allelic variants in INSL3 yielded several mutations, only one of which (P49S) reduced INSL3 binding to RXFP2.[99] Mutation analysis of the *RXFP2* gene revealed a single mutant T222P allele found in 3% of patients and no controls. The mutant allele produces a nonfunctional receptor unable to respond to ligand stimulation in vitro.[97] Thus, in some patients it appears that an abnormal gubernaculum plays a role in the testicular maldescent. These genes may work in concert to help control testis development and migration, but mutations involving these two genes do not represent a frequent cause of UDT in humans.

Homeobox Genes

HOX genes play a key role in the morphogenesis of segmental structures along the anterior posterior body axis.[100] These genes act as master regulatory switches or transcription factors that specify axial identity and control the growth and differentiation of cells related by position. Murine *hoxa10* knockout male mice exhibited bilateral cryptorchidism with developmental abnormalities of the gubernaculum and resultant abnormal spermatogenesis and infertility.[101,102] Similarly, mice homozygous for *hoxa11* deletions are also infertile and cryptorchid.[103] Hormonal disruption was likely not the cause of UDT in these knockout mice, as they appeared normally masculinized. In situ hybridization for *hoxa10* transcripts in wild-type mice indicate that this gene is expressed in the gubernacular cord and bulb, but not in other tissue of the male reproductive tract.[101] Branford et al. found that the reproductive tracts of *Hoxa10* or *Hoxa11* single heterozygous mutants were normal, but male transheterozygotes (*Hoxa10*± and *Hoxa11*±) displayed UDT and tortuous ductus deferens, similar to what is seen with the knockouts of these genes.[102] *Hoxa10* and *hoxa11* appear to be functionally redundant in the development of the male reproductive tract, such that a quantitative loss of any two *hoxa10/hoxa11* alleles results in similar testicular anomalies. It is likely that *hox11* is important for gubernaculum function, as mice with *hox11* mutations exhibited abnormal gubernacula that failed to migrate.[104]

Several human studies have been conducted to evaluate the association between allelic variants in *HOX* genes and UDT. Allelic variants in *hox13* have been shown to be increased in subjects with cryptorchidism compared with controls.[105] Similarly, Kolon et al. found that out of 45 boys, five missense mutations and one large deletion were found in exon 1 of *HOXA10*, which represented a statistically significant elevation in allelic variants in the UDT group compared with controls.[47] However, in a smaller study, Bertini et al. examined exons 1 and 2 of *HOXA10* for allelic variants in 18 patients with UDT and 28 healthy controls. The same allelic variant was detected at similar levels in cases and controls.[48] Further evaluation should be carried out to fully characterize the role of these posterior *HOX* genes in abnormal testicular descent. Many other gene products have been targeted as being expressed in testicular differentiation (i.e., *PAX5*, *SRY*, *SOX9*, *DAX1*, and *MIS*) but not specifically in cryptorchidism (for review, see Hughes[106] and Nudell and Turek[107]).

Hormonal Factors

It has been theorized that this spontaneous descent in infancy may occur due to the normal gonadotropin surge that occurs around 60–90 days of life.[41,108–110] Job et al. and Gendrel et al. reported that this surge is blunted in boys with UDT that remain undescended in the first year of life.[108,109] They demonstrated a significant difference in the polynomial regression curves, comparing the testosterone levels of persistently cryptorchid testes with those having delayed spontaneous descent. However, the positive predictive value that bilateral UDT will have abnormally low testosterone levels is only about 23%. Recently, Iwatsuki et al. reported that peripubertal boys with hypospadias and cryptorchidism had higher levels of FSH than controls.[111] In contrast, Barthold et al. examined gonadotropin and testosterone, estradiol, inhibin B, leptin, and sex hormone–binding globulin in a cohort of cryptorchid boys. They failed to identify any significant differences in hormonal levels in their cohort compared with controls.[112]

An endocrine disruptor is an environmental chemical that interferes with the production, transport, and metabolism of hormones in the body. Some of these agents have estrogenic activity, while others act as agonists and antagonists of androgens. Endocrine disruptors have been hypothesized to play a role in cryptorchidism, as androgens contribute significantly in the physiology of germ cell development and testicular descent. Several environmental chemicals have antiandrogenic effects in rodent models. Although these agents act by many different mechanisms, they all produce similar effects on the developing male reproductive tract. At high *in utero* doses, antiandrogens are associated with UDT and agenesis of the epididymis, while at lower doses, hypospadias and decreased anogenital distances are seen. Boys exposed to the antiandrogenic effects of diethylstilbestrol *in utero* have an increased number of genital abnormalities, including cryptorchidism.[113]

Phthalate esters inhibit testosterone synthesis during fetal life and produce dose-related abnormalities of the male reproductive tract, such as focal hyperplasia of fetal Leydig cells that persists postnatally, as well as agenesis of the gubernaculum.[114–117] Findings with the phthalates are of particular concern because exposure is ubiquitous and phthalates are widely used in many consumer products. The phthalate monoester metabolites

have been found in urine samples of >75% of approximately 2550 participants in the 1999–2000 National Health Nutrition and Examination Survey.[118] In animal models, phthalates reduce cholesterol transport across the mitochondrial membrane, decrease testosterone biosynthesis, and reduce expression of the *insl3* gene.[119–121] Animal research findings demonstrate a coordinated, dose-dependent reduction in the expression of key genes involved in cholesterol transport and steroidogenesis, and a corresponding reduction in testosterone in fetal testes at low dibutyl phthalate (DBP) doses, which do not produce male reproductive tract anomalies.[114] Similar studies have been carried out in adult rats to determine the pattern of gene expression in the proximal Wolffian duct, which gives rise to the epididymis, following prenatal exposure to DBP. Changes in mRNA expression were observed in genes involved in testosterone biosynthesis and testicular descent, including the insulin-like growth factor pathway and the androgen receptor.[122] These alterations in expression of genes at phthalate doses that do not produce isolated UDT suggest that gene–environment interactions could occur in human populations. It has been hypothesized that fetuses with susceptible genotypes exposed *in utero* to environmentally relevant doses of phthalates may be at the greatest risk for developing UDT. Familial clustering of hypospadias and UDT among first-degree relatives has been suggested as evidence for a genetic component for these anomalies. However, another etiologic possibility is the role of exposure to environmental contaminants in familial clusters because of the high probability of shared exposures among first-degree relatives.[123]

These animal findings further advocate a multifactorial and complex etiology of cryptorchidism. UDT is a variable and multifactorial phenotypic trait that likely involves several candidate genes and hormonal and environmental risk factors, rather than a causative single gene mutation. It is likely that a perturbation in the dynamic equilibrium of these factors is involved in the pathogenesis of cryptorchidism.

DIAGNOSIS

History and Physical Exam

A thorough history should include prematurity (the incidence of UDT in premature boys is as high as 30%), maternal use or exposure to exogenous hormones (estrogens), lesions of the central nervous system (myelomeningocele), and previous inguinal surgery. Document a family history of cryptorchidism and other congenital anomalies, neonatal deaths, precocious puberty, infertility, and consanguinity. It is also important to know if the testes were ever palpable in the scrotum at the time of birth or within the first year of life. Testicular retraction, due to a strong cremasteric reflex, is most apparent between 4 and 6 years of age and may lead to an inaccurate diagnosis of UDT.

An undescended testis can be classified by its location. It may be located in the abdomen, the inguinal canal, the superficial inguinal pouch, the upper scrotum, or rarely, in an ectopic location (perineum, contralateral scrotum, or femoral). However, for treatment purposes, the main distinction that needs to be made is whether the testis is palpable.

The patient should be examined supine in the frog leg position with both legs free. With warmed hands, check the size, location, and texture of the contralateral descended testis (CDT). Begin examination of the UDT at the anterior superior iliac spine and sweep the groin from lateral to medial with the nondominant hand. Once the testis is palpated, grasp it with the dominant hand and continue to sweep the testis toward the scrotum with the other hand. With a combination of sweeping and pulling, it is sometimes possible to bring the testis to the scrotum. Maintain the position of the testis in the scrotum for a minute, so that the cremaster muscle is fatigued. Release the testis, and if it remains in place, it is a retractile testis. If it immediately pops back to a prescrotal position, it is a UDT.

For the difficult-to-examine patient (chubby 6-month-olds or obese youths), the sitting cross-legged position or the baseball "catcher's position" can also help relax the cremaster muscle. Wetting the fingers of the nondominant hand with lubricating jelly or soap can increase the sensitivity of the fingers in palpating the small, mobile testis.

A retractile testis is often confused with a UDT. The key to distinguishing a retractile testis from a UDT is demonstrating that the testis can be delivered into the scrotum. The retractile testis will stay in the scrotum after the cremaster muscle has been overstretched, while the low UDT will immediately pop back to its undescended position after being released. If there is any question, the child should be seen in follow-up for a repeat exam. Miller et al. have also recommended the use of hCG stimulation to help distinguish between a retractile and an undescended testis in the hard-to-examine child.[124]

In one series, more than 70% of UDT are palpable.[125] That leaves approximately 30% of testes that cannot be localized by physical exam. For testes that are not palpable, approximately 30% will be found in the inguinal-scrotal area, 55% will be intra-abdominal, and 15% will be absent or "vanished."[125–127] An atrophic or vanishing testis can be found anywhere along the normal path to the scrotum. The etiology is thought to be due to neonatal vascular ischemia, possibly due to torsion.[128] The CDT may be hypertrophied in these boys; however, hypertrophy of the contralateral testis is not an unequivocal sign that the nonpalpable testis is vanished or a nonfunctional nubbin.

Initial diagnostic laparoscopy or inguinal exploration will identify a viable testis or confirm an absent testis by revealing blind-ending spermatic vessels or a nonviable nubbin.[129–133] Upon surgical exploration, 60%–80% of nonpalpable testes are present in the inguinal canal or in the intra-abdominal location, while up to 40% are absent or are an inguinoscrotal nubbin of fibrous tissue and hemosiderin. The presence of bilateral UDT should raise suspicion of an endocrine disorder or an intersex state that should be evaluated. Cryptorchidism associated with hypospadias, especially proximal, should also raise the possibility of the intersex state and occurs in 30%–40% of patients, mainly consisting of defects in the testosterone synthesis pathway.[134]

Laboratory Tests

In boys with unilateral or bilateral UDT where one testis is palpable, no further laboratory evaluation is necessary to aid the diagnosis. In boys with bilateral UDT where neither testis is palpable and also in boys with associated hypospadias, chromosomal and endocrinologic evaluation may be carried out but is not always necessary.[44] These levels should be drawn during the maternal newborn gonadotropin surge or at 60–90 days of life. In patients 3 months or younger with bilateral nonpalpable UDT, LH, FSH, and testosterone levels will help determine whether the testes are present. After 3 months of age, an hCG stimulation test will aid in the diagnosis of the absent testes. A weight-based single injection of hCG (100 IU/kg) is usually sufficient to detect a rise in serum testosterone 4–5 days later.[135] A failure to see a measurable increase in testosterone, in combination with elevated LH and FSH, is consistent with the diagnosis of anorchia.[136,137] MIS may be a more sensitive and specific prepubertal marker for detecting the presence of testes. Lee et al. found that serum MIS correlates with testicular tissue. A measurable value is predictive of nonpalpable UDT, while an undetectable value is highly suggestive of anorchia but warrants further investigation, such as hCG stimulation.[138] It should be noted that both MIS and testosterone levels may be misleading in cases of UDT with a disorder of sex development if the testes are severely dysgenetic or there is a mutation of the anti-Müllerian hormone or receptor genes. Thorup and colleagues further refined the serologic evaluation of bilateral nonpalpable testes. There are preliminary data that a single serum sample, without hCG stimulation, which demonstrates low inhibin B and elevated gonadotropins, is indicative of bilaterally absent testes or nonfunctional nubbins.[139]

Imaging

Hrebinko and Bellinger found that the most reliable mode of exam has been the physical exam by a pediatric urologist (84%) compared with a referring physician (53%). The accuracy of the radiological exam was 44%, and the study did not influence the management decision in any of the cases.[140] Despite the primacy of the physical exam, ultrasound is ordered quite frequently in the initial evaluation of the boy with cryptorchidism.[141] However, the routine utilization of ultrasound is unnecessary. Tasian and Copp analyzed the diagnostic performance of ultrasound in the evaluation of nonpalpable UDT. They found that the sensitivity and specificity of ultrasound in correctly identifying a nonpalpable testis were 45% and 78%, respectively. Accordingly, a positive ultrasound increases and a negative ultrasound changes the probability that a nonpalpable testis is located within the abdomen from 55% to 64% and 49%, respectively. These results indicate that preoperative ultrasound does not reliably localize nonpalpable testes and is not useful in determining the surgical management of these patients.[142]

Early studies have shown that computed tomography (CT) can localize UDT; however, many of the testes seen on CT were potentially palpable in the inguinal canal.[143,144] Recent studies have demonstrated the risk of secondary malignancies conferred by ionizing radiation, which is especially pronounced in the pediatric population.[145] While CT has an important role in the staging of testis cancer, for which boys with a history of cryptorchidism are at risk, there is no role for routine CT evaluation of boys with UDT.

MRI has greater diagnostic performance than ultrasound for localizing nonpalpable testes. Yeung et al. employed gadolinium-enhanced magnetic resonance angiography (MRA) to identify 100% of canalicular UDT and 96% of intra-abdominal UDT (one missed vanishing testis).[146] Eggener et al. performed a hypothetical protocol of MRA with observation of testicular nubbins, and nearly one-third of the boys avoided surgery without any increased cost of care.[147] More contemporary studies that have utilized conventional MRI in conjunction with diffusion-weighted MRI to identify nonpalpable testes have demonstrated similar performance characteristics. In this series, conventional MRI had a sensitivity of 85% and a specificity of 87.5%. When combined with diffusion-weighted imaging, the sensitivity increased marginally to 89.5% and the specificity remained the same. However, even for MRI, not identifying a testis does not completely exclude its absence.[148,149] Currently, for nonpalpable testes open inguinal exploration or laparoscopy is necessary to confirm the presence of testes.

TREATMENT

Hormonal Therapy

Primary hormonal therapy with hCG or gonadotropin-releasing hormone (GnRH) (or LH-releasing hormone [LHRH]) has been used for many years, especially in Europe. The action of hCG is virtually identical to that of pituitary LH, although hCG appears to have a small degree of FSH activity as well. It stimulates production of gonadal steroid hormones by stimulating the Leydig cells to produce androgens. The exact mechanism of action of the increased androgens in testicular descent is not known, but it may involve effects on the testicular cord or cremaster muscle. This medication is administered by intramuscular injection. Multiple series have been published, but due to differences in patient age, treatment schedules, and the possible inclusion of retractile testes, very divergent results have been reported.

Many dosage schedules are reported, ranging from 3 to 15 doses.[150–153] However, hCG appears to be as effective in 3 or 4 doses as in 9 or 10 doses. One of the most common schedules is 250 IU/dose in young infants, 500 IU/dose up to 6 years old, and 1000 IU/dose greater than 6 years old given twice a week for 5 weeks (International Health Foundation). Success rates for descent into the scrotum are 25%–55% in uncontrolled studies, but only 6%–21% in randomized, blinded studies. Distal inguinal testes in older boys are more likely to descend in response to hormonal treatment than abdominal testes. Repeated courses have offered little advantage. Side effects of hCG treatment include increased scrotal rugae, pigmentation, pubic hair, and penile growth, which regress after treatment

cessation. A total dose of more than 15,000 IU must be avoided since it may induce epiphyseal plate fusion and retard future somatic growth.

Agonistic analogues of GnRH, such as nafarelin or buserelin, stimulate the release of the pituitary gonadotropins, LH and FSH, resulting in a temporary increase of gonadal steroidogenesis. Repeated dosing abolishes the stimulatory effect on the pituitary gland, and twice daily administration leads to decreased secretion of gonadal steroids by 4 weeks. These hormones are available as a nasal spray but are only approved for the treatment of cryptorchidism in Europe. Interpretation of results is again tainted by multiple treatment strategies. Success rates in uncontrolled studies range from 13% to 78%, while better-controlled investigations resulted in 6%–38%.[153,154] Rajfer et al. conducted a randomized, double-blind study comparing hCG 3300 IU per week for 4 weeks with GnRH spray 200 μg six times a day for 4 weeks. Descent into the scrotum occurred in 6% of the hCG group and 19% of the GnRH group.[152] Several authors have recommended combined GnRH-hCG hormonal treatment. Lala et al. administered LHRH 1.2 mg/day for 4 weeks and nonresponders also received hCG 500 IU three times a week for 3 weeks. After combined treatment, 38% of testes descended.[154] Bica and Hadziselimovic treated patients with a low dose of buserelin 20 μg as a daily spray for 28 days, followed by hCG for failures. Twenty-six percent of the testes descended with the spray alone, while hCG increased the descent to 37%.[155] Hadziselimovic et al. advocated initial treatment with GnRH spray 400 μg tid into each nostril for 4 weeks, followed by salvage treatment for failures with hCG 1500 IU/week for 3 weeks. A success rate of 56% with GnRH was increased to 65% with the addition of hCG.[156]

The recognized side effects of increased androgens, including increased penile or testicular size, scrotal erythema, or erections, seem to be less with GnRH than hCG. Initial treatment with GnRH may deserve some consideration since it is administered as a spray rather than an injection. Even in 20% of patients, it may aid descent in more distal testes, make intra-abdominal testes palpable, or help differentiate retractile from true UDT. Hormonal therapy may also have a beneficial effect on fertility indices.[157] It has been shown that use of LHRH analogue in boys with very severe histological changes in the testis (total germ cell count of less than 0.2 germ cells/tubule in UDT and less than 0.6 germ cells/tubule in CDT) has an advantageous effect on the developing germ cells. In a study by Huff et al., patients who had no germ cell count on the biopsy did not show improvement after hormonal therapy, but those who had some germ cells demonstrated improvement.[158] This improvement in germ cell count and maturation may eventually reflect a better prognosis for fertility. GnRH, LHRH, and hCG administration prior to orchiopexy has been shown to improve the fertility index on histopathologic analysis of biopsies obtained at the time of orchiopexy.[159,160] Although it is unknown if this effect on testis histology persists into adulthood or disappears once the hormonal stimulus is removed, Hadziselimovic and Herzog showed that men who were treated in childhood with hormones had better semen analyses than men who had childhood orchidopexy alone or placebo treatment.[161]

LONG-TERM PROGNOSIS

Patients with cryptorchidism have two major concerns. They have an increased incidence of developing testicular cancer and also a heightened risk of subfertility.

Testicular Malignancy

Men with a history of cryptorchidism have an increased risk of testicular cancer. The increased incidence of malignancy in cryptorchid testes varies from 49/100,000 (0.05%) to 12/1075 (1%).[162] Early reports stated a significantly higher risk of carcinoma in an abdominal testis; however, inclusion of boys with abnormal karyotypes or genitalia may have biased the results.[163] Although one postulate is that the etiology of the testicular cancer is related to the abnormal position of the testis, the mild increase in cancer in the contralateral descended mate argues for an intrinsic testicular abnormality as the cause. The increase in incidence of malignancy in the cryptorchid testis warrants close follow-up, especially after puberty. Every cryptorchid boy should be taught how to perform a monthly testicular self-examination in order to try to enable early detection. Although the historical teaching has been that orchiopexy does not decrease the risk of testicular cancer, more recent studies have demonstrated that orchiopexy performed before puberty decreases the risk of testis cancer compared with in those boys with cryptorchidism who undergo orchiopexy after puberty. However, the risk of testis cancer does not decrease to that of normal controls even when orchiopexy is performed at an early age.[164,165]

Fertility

Formerly bilaterally cryptorchid men have greatly reduced fertility compared with unilateral cryptorchids and the general male population.[3] Lee et al. showed a paternity rate of 62% (38% infertile) in formerly bilaterally cryptorchid men compared with a matched control group of 94% (6% infertile), indicating a six times increased risk.[166] In contrast, unilaterally cryptorchid men had a paternity rate of 89.5%, which is similar to the level of infertility found in other studies of the general population.[167] Examination of subfertility, or time to pregnancy, shows that bilaterally cryptorchid men have greatly increased waiting times to pregnancy (33.9 months compared with 11.1 months for unilaterals and controls). Lee et al. also examined the association of pretreatment testis location with fertility rates and various hormone levels (inhibin B, LH, FSH, and testosterone) in adulthood.[168] They concluded that "preoperative testis location in men with previous unilateral cryptorchidism is not a major determinant of fertility according to paternity, sperm count, or hormone levels." A prepubertal Ad spermatogonia count or other as yet unidentified molecular markers may be more useful indicators of fertility (and paternity) in these patients. Further investigation is needed concerning sperm motility, morphology, and function.

SUMMARY

Research efforts to define the pathophysiology of cryptorchidism and its sequelae have rapidly advanced in the past 10 years. Surgical techniques have been so refined that today 6-month-old cryptorchid boys are safely and successfully repaired. Further studies will be aimed at identifying those boys that are at increased risk for future infertility or malignancy in order to intervene early and change their outcome.

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CHAPTER 80

Surgical Treatment

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INTRODUCTION

The goals of all surgical therapy for cryptorchidism are preservation of fertility, repair of patent processus vaginalis, and relocation of a viable testicle to the scrotum in a tension-free manner. The first step of management is performing an exam under anesthesia and confirming whether a testicle is palpable. One study found that up to 18% of boys who were thought to have a non-palpable testis had a palpable gonad when examined under anesthesia,[1] negating the need for intra-abdominal exploration.

SURGICAL MANAGEMENT OF PALPABLE TESTIS

Inguinal Orchiopexy for the Palpable Testis

The key steps of this procedure are (1) complete mobilization of the testis and spermatic cord, (2) repair of the patent processus vaginalis, (3) preservation of vascular integrity while mobilizing the spermatic cord to achieve tension-free placement of the testis within the dependent position of the scrotum, and (4) fixation of the testis in the scrotum.

A transverse inguinal skin incision is made in the midinguinal canal, usually in a skin crease in children younger than 1 year of age (Figure 80.1). The dermis is opened with electrocautery, and subcutaneous tissue and Scarpa's fascia are opened sharply, taking care to avoid the testis, which is found deep in the scarpas and usually superficial to the external oblique fascia in the superficial inguinal pouch. Sharp dissection cleans the surface of the external oblique fascia of prefascial fat, and gentle spreading over Poupart's ligament defines the full lateral extent of the external oblique fascia (Figure 80.2). This maneuver is helpful to maintain anatomic orientation in defining the area directly over the inguinal canal.

If the testis is intracanalicular and not lying in the superficial inguinal pouch, the external oblique fascia is opened with a small superficial incision that is carried through the external ring, with care taken to preserve the ilioinguinal nerve. Once identified, the tunics overlying the testis are grasped, and the distal gubernacular attachments are sharply dissected. Cremasteric muscular fibers and any anomalous fibrous attachments from the superficial peripheral fascia are then dissected sharply away from the testis and spermatic cord (Figure 80.3). Once the spermatic cord is freely mobilized from cremasteric attachments in the inguinal canal, the tunica vaginalis is opened over the testis (Figure 80.4).

Complete mobilization of the spermatic cord is essential to achieve adequate cord length for tension-free placement of the testis into the scrotum. This should not be done at the risk of devitalizing the vascular supply to the testis or damaging paratesticular structures, including the vas deferens. The key steps in this part of the operation include (1) complete transection of the fused fibers between the cremasteric muscle and the internal oblique muscle; (2) dissection of internal spermatic fascia from the cord structures (Figure 80.5); and (3) complete separation of the patent processus vaginalis from the elements of the spermatic cord, with mobilization and ligation of the hernia sac and peritoneum to at least just inside the internal ring (Figure 80.6). In most cases, division of the processus vaginalis and cremasteric muscle attachments, and separation of the vas from the vascular cord elements provide adequate cord length to allow for placement of the testis in the scrotum. Additional cord length may also be obtained by bluntly dissecting the spermatic vessels from the lateral spermatic fascia with the aid of a Ragnell retractor in the internal ring and a Q-Tip or Kittner dissector. While performing the retroperitoneal dissection, the external oblique may be opened above the level of the internal ring, and the internal oblique muscle can be divided 1–2 cm from the superior lateral margin of the internal ring.

Once adequate cord length has been obtained, the testis must be placed into the scrotum in a tension-free manner. Experimental evidence has documented that transparenchymal suture fixation causes testicular damage by inducing an inflammatory reaction regardless of suture size and material. In comparison, dartos-fixed testes demonstrated complete circumferential adherence, with minimal inflammation and preserved spermatogenesis.[2,3] Based on these studies, securing the testis to the scrotum with a suture violating the testis is avoided. When short-term external fixation to a nylon button is required due to tension, or the operator prefers intrascrotal suture fixation, the suture should traverse the fibrous tissue beneath the lower pole of the testis. It is important to be familiar with the intragonadal vascular anatomy, especially when ligation of the spermatic vessels is contemplated. The collateral arterial circulation through the deferential artery, which

FIGURE 80.1 Initial incision in transverse skin crease.

FIGURE 80.2 Exposure of the external oblique fascia.

communicates with the internal spermatic arterial system both in the spermatic cord and at the lower pole of the testis, was found to be compromised in all testes with placement of a transgonadal traction suture.[4]

In order to place a testis in a dartos pouch, a transverse midscrotal superficial skin incision is made within a rugal skinfold (Figure 80.7), and a mosquito hemostat is then used to develop a tissue plane just under the scrotal skin superficial to the dartos layer. The scrotal pocket should be developed from the median raphe and the lateral scrotal margin (Figure 80.8), with creation of the space in the inferior and anterior portion of hemi-scrotum which allows for fixation of the testis in a prominent, dependent position. After the testis and cord are completely mobilized and the tunica vaginalis is opened fully over the testis, a hemostat is passed just over the pubic symphysis

FIGURE 80.3 Creamsteric and fibrous attachments are freed from the spermatic cord.

FIGURE 80.4 The tunica vaginalis is opened, delivering the testis from the hernia sac.

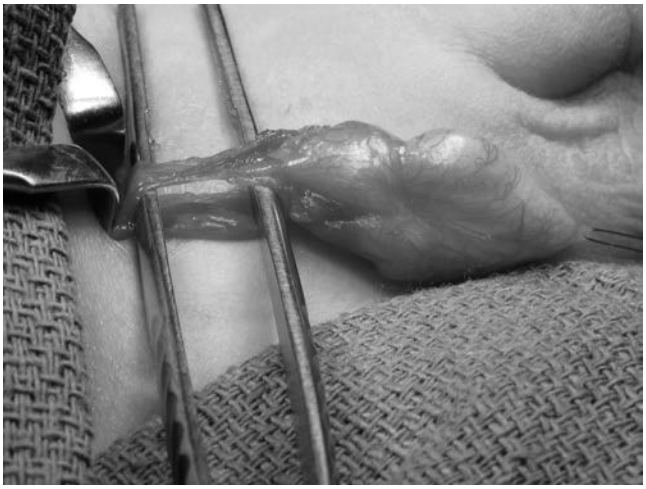


FIGURE 80.5 Hernia sac and lateral spermatic fascia is mobilized from the spermatic cord.

FIGURE 80.6 Ligation of the hernia sac at the level of the internal ring.

FIGURE 80.7 Transverse scrotal skin crease incision.

FIGURE 80.8 Superficial pouch in anterior dependent portion of scrotum.

FIGURE 80.9 Traction suture passed subcutaneously.

from the inguinal incision through the tough dartos fascia into the scrotum. It is important to pass the hemostat into the medial aspect of the scrotum to avoid lateral placement or migration of the testis. The most direct path to the scrotum allows for the most dependent placement of the testis. A second hemostat is back-passed from the scrotum into the inguinal incision; the most dependent tunica vaginalis or remnant of gubernaculum is grasped (Figure 80.9), and the testis is passed into the scrotum (Figure 80.10), with care taken to avoid torsion of the spermatic cord.

The dartos fascial window is closed with a fine absorbable suture, with the option of placing this suture through the redundant tunica vaginalis well above the level of the testis in order to indirectly secure the cord at this position. Closing the dartos layer behind the spermatic cord redefines the floor or inferior aspect of the superficial pouch. The testis is then placed within the dartos pouch, and the scrotal skin closed with fine interrupted absorbable sutures, such as 4-0 chromic vertical mattress sutures. The external oblique fascia is closed with running or interrupted absorbable suture with re-creation of the external ring, taking care to avoid impingement of the spermatic

FIGURE 80.10 Passage of testis into the right hemiscrotum.

FIGURE 80.11 Final postoperative appearance.

cord. For skin closure, we prefer an interrupted subcuticular closure with fine absorbable suture and placement of a flexible liquid dressing, such as Dermabond (Figure 80.11).

Scrotal Orchiopexy for the Palpable Testis

Although inguinal orchiopexy represents the traditional approach to the palpable undescended testicle, many of us now use a single scrotal incision for the vast majority of these cases. The high scrotal orchiopexy was first published in 1989,[5] and in early descriptions involved a high scrotal or inguinal scrotal incision.[6,7] In these early series, it was felt that it was more difficult to dissect the hernia sac from the cord, that high ligation of the hernia was difficult, and the complication rate appeared to be higher than that of traditional approaches. In addition, there was concern about the lack of a retroperitoneal dissection, which had classically been considered a vital part of adequate orchiopexy. In the 1990s, we modified that approach, suggesting that a scrotal incision can be used for palpable ectopic testes and in older children with testicular ascent.[8] In the original description of the "low scrotal" approach, an inguinal incision was used if a patent processus was identified. We found that by using careful patient selection, the likelihood of identifying a hernia was approximately 20%. Over the past decade, this technique has been extended to all but the highest of palpable testes, and hernias identified are corrected through the scrotal incision. There is experience with hundreds of procedures performed through a single scrotal incision, with no evidence of increased risk of hernia recurrence and with excellent outcomes.[9]

The technique of scrotal orchiopexy is reasonably straightforward. First, the testis does not need to reach the scrotum in order to use this approach; the scrotum must be able to reach the level of the testis. An anterior horizontal scrotal incision is made with scalpel or electrocautery. Blunt dissection is used to expose the anterior processus. The testis within its coverings is brought out through the incision, and separated from attachments up to the external ring. The anterior processus is then opened, and patency assessed. Whether or not there is a patent processus, the posterior wall is separated from the vessels and vas deferens in order to release the intrinsic cord length. If there is a hernia, it is separated from the cord well into the external ring, and then suture ligated. At this point, any ectopic attachments that can be isolated from the vessels and vas deferens are divided, and after this maneuver, there is almost always enough length to reach the dependent scrotum. The testis is fixed in the scrotum by whatever method is preferred by the operator.

OPEN APPROACHES TO HIGH OR INTRAPERITONEAL TESTES

Jones Approach for the High Undescended Testis

A high inguinal approach or Jones incision is an open surgical alternative for the high canulicular or intra-abdominal testis.[10] This procedure shares similar indications and surgical principles with laparoscopic orchidopexy, and was the popular surgical approach prior to the advent of laparoscopic management of the intra-abdominal testis; now it is used by some practitioners to manage high palpable testes. Principles include preservation of the spermatic vessels, high retroperitoneal mobilization of the spermatic vessels, and passage of the testis directly through the abdominal wall at the pubic tubercle (Prentiss maneuver). The procedure may also be performed in combination with laparoscopy to help locate the testis and aid in dissection. A transverse incision is made medial to the anterior superior iliac spine and is carried down to the external oblique fascia just superior to the internal ring. Once the fascia is incised, a muscle-splitting technique is used to expose the retroperitoneum and mobilize the peritoneum medially. The internal ring and processus vaginalis, if present, are identified and the peritoneum opened at this level, delivering the testis into the field. Once the hernia sac is ligated, the spermatic vessels are dissected from the lateral spermatic fascia as cranial as possible and a Prentiss maneuver is performed by passing the testis under the floor of the inguinal canal to an exit site just above the pubic tubercle. If there is tension on the testis after delivery into the subdartos pouch, an external nylon fixation button helps maintain a dependent scrotal position.

Open Fowler–Stephens Orchiopexy

Division of the testicular vessels in cases of high inguinal or intra-abdominal testis was first described in 1899 by Bevan.[11] However, it was not until 1959 that Fowler and Stephens devised a means to repair the high undescended testis while preserving its blood supply via collateral circulation from the deferential artery and the cremasteric system.[12]

The technique described by Fowler and Stephens was originally a one-stage procedure, but it may also be performed in two stages. If a one-stage repair is to be performed, it is critical early in the dissection that a wide pedicle of peritoneum be preserved with the vas deferens in order to maintain collateral blood flow. It is also

important to remember that the testis is technically a retroperitoneal organ, as is its blood supply and that of the vas deferens.

The technique begins with a high transverse inguinal incision that is carried down to the external oblique fascia. This is opened, allowing access to the inguinal canal and the peritoneum. The peritoneum is opened and the testis is mobilized without transecting any structures proximal to the testis. Once it has been determined that the spermatic vessels will not traverse the distance to the scrotum, they are divided.

The original one-stage procedure is dependent on a long looping vas; however, this has been reported in less than one-third of boys with true intra-abdominal testes.[12] If the patient's anatomy permits, the testicular artery is divided high above the testis followed by mobilization of a wide swath of peritoneum leaving the medial peritoneum between the testis and vas undisturbed. If further length is required, the vas may be straightened by dividing the peritoneum between the redundant vas. The course of the vasal pedicle should be as medial as possible in order to choose the shortest distance to the scrotum which may require a direct placement of the testis and pedicle through a neohiatus in the abdominal wall over the symphysis pubis, or medial to the inferior epigastric vessels. From this point forward, the procedure is carried out as a standard orchiopexy with creation of a dartos pouch with the exception that a nylon fixation button is often necessary.

The anticipated advantage of a two-stage orchiopexy with spermatic vessel ligation is twofold: (1) to allow for development of the collateral blood supply to compensate for division of the main blood supply to the testis, and (2) to allow for greater mobility of the testis in order to place it within the scrotum.[13,14] The two-stage Fowler–Stephens orchiopexy is typically performed by ligating the spermatic vessels in situ as close to the origin as possible, and then returning after 6 months or longer to complete the vasal-peritoneal pedicle mobilization using the standard Fowler–Stephens technique. Koff and Sethi reported excellent results with a technique of low spermatic vessel ligation and demonstrated that high ligation of the spermatic vessels does not need to be performed to preserve testicular viability.[15]

Surgical Management of Nonpalpable Testis

Nonpalpable testis accounts for approximately one-fifth of children with an undescended testis. There are numerous reports attesting to radiographic means of evaluating undescended testis; however, it remains a surgical diagnosis given the low sensitivity and specificity of ultrasound (45% and 77%[16–20]) and the expense, limited availability, and need for sedation with MRI.[20,21] Diagnostic laparoscopy has been used for more than 35 years to identify the presence and location of the nonpalpable testis.[22] Belman and colleagues first reported that 30%–50% of nonpalpable testis will be absent, the majority of which are due to prenatal torsion in the inguinal canal or scrotum. Evidence of prenatal torsion will most commonly be identified as a hemosiderin-laden and/or calcified nubbin on scrotal exploration.[23] Contemporary series support the finding that 55%–65% of patients will have vas and vessels that enter the inguinal canal, although the need for inguinal exploration remains controversial.[24] The quality of laparoscopic images also offers an accurate assessment of the surrounding anatomy and testicular viability, which has a reported accuracy of greater than 95%.[15,16] The accuracy and quality of the information obtained from laparoscopy allows for definitive management or planning of further surgical approaches in the majority of primary undescended testes[25] and in children who have undergone a previous inconclusive open exploration.[26–28]

Diagnostic Laparoscopy for the Nonpalpable Testis

Technique

Diagnostic laparoscopy begins by gaining access to the abdomen with a Veress needle or the preferred open technique. In the classic open technique, a semilunar umbilical incision is carried down to the rectus fascia. The fascia is opened and the peritoneum is sharply incised, allowing the trocar to be placed between the obliterated umbilical arteries. Alternatively, access is gained through a small intraumbilical incision, entering directly into the attached peritoneum at the base of the umbilicus, and using a radially dilating trocar to establish an airtight seal.[29,30] A 5 mm laparoscope is available in most pediatric hospitals, but smaller-diameter laparoscopes with improved optics are becoming more widely available.

Laparoscopic Assessment

Once the camera has been placed, the possible findings in regard to testicular position and inguinal anatomy are

1. Blind-ending vas deferens and vessels above the internal ring (vanishing testis) (Figure 80.12)
2. Cord structures entering the internal ring (viable intracanulicular testis vs. intracanulicular or scrotal atrophic testis) (Figure 80.13)
3. Intra-abdominal testis (Figure 80.14)
4. Testicular agenesis

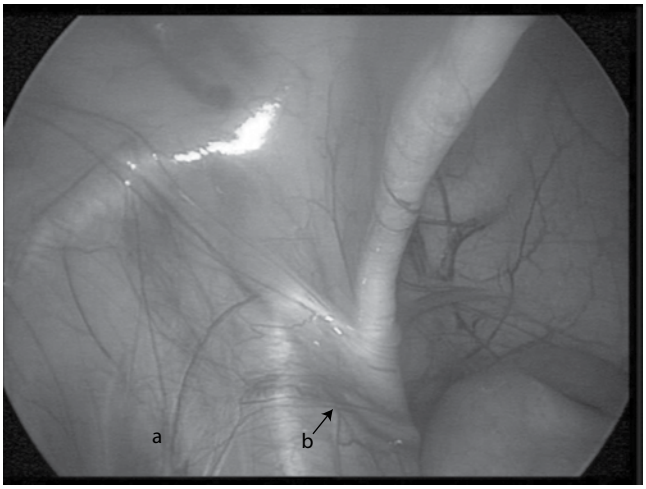


FIGURE 80.12 Finding blind ending and divergent testicular vessels (a) is evidence of a vanishing testicle. The sole finding of a blind ending vas (b) is insufficient evidence to conclude that there is absence of ipsilateral testicular tissue.

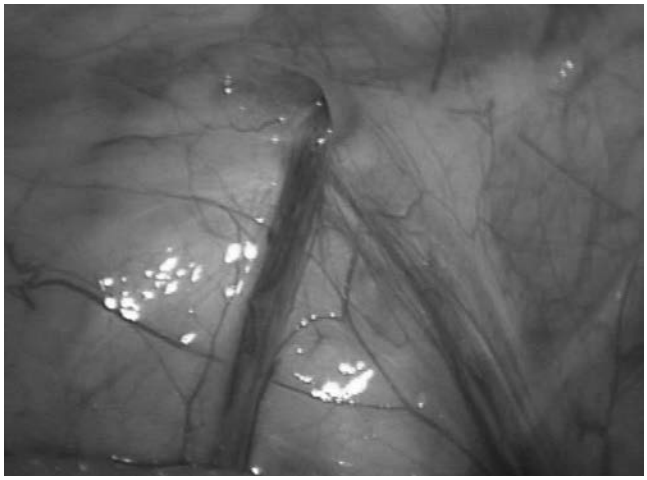


FIGURE 80.13 Laparoscopic view of a left patent processus vaginalis (hernia) with normal cord structures exiting the internal ring.

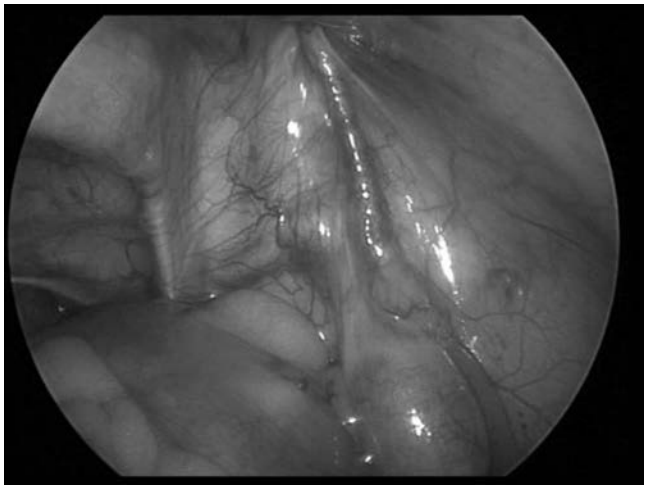


FIGURE 80.14 A Right intra-abdominal testicle >2 cm from the internal ring.

Approximately 36%–64% of children presenting with a unilateral nonpalpable testis will be monorchid.[1,31–37] A vanishing testis is most commonly due to an in utero torsion or compromising vascular event that may have occurred anywhere along the path of decent, but most commonly occurs in the inguinal canal or scrotum. An intra-abdominal vanishing testis will demonstrate the classic anatomy of atretic blind-ending vas and spermatic vessels, usually within a few centimeters of the internal ring. Nonunion of the vas and the testis can occur, so visualization of a blind-ending vas deferens in the absence of vessels is not adequate to make the diagnosis of a vanished testis. In cases of an inguinal or scrotal event, the vessels and vas may be seen entering the inguinal canal, but they will be markedly attenuated when compared with the contralateral side. When blind-ending spermatic vessels are found, no further surgical intervention is necessary. Some investigators have recommended a transscrotal testicular fixation procedure on the normally descended contralateral testis because of the reported risk of abnormal testicular fixation (bell clapper deformity),[38,39] although most feel that this is unnecessary, as prenatal testicular torsion is generally an extravaginal event and should not correlate with increased contralateral risk after the neonatal period.

Management of atretic vessels and vas that enter the inguinal ring is a controversial topic. Atretic vessels are predictive of a nonviable testicular remnant, which will most often demonstrate histological evidence of ischemia and necrosis (fibrosis, hyalinization, calcification, and hemosiderin deposition). There have, however, been reports of viable testicular elements, including residual seminiferous tubuals and germ cells, in up to 13% of testicular remnants.[40–45] Carcinoma in situ has not been reported within these specimens, and it has been argued that the risk of malignant degeneration is remote.[43] Exploration and removal of the atrophic elements therefore appear unnecessary; however, much latitude is granted on the subjective nature of distinguishing between atretic and normal vascularity.

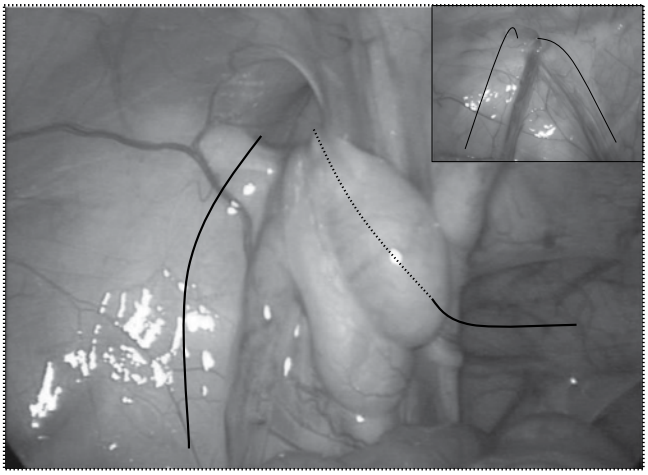
Normal internal spermatic vessels are indicative of an intracanalicular testis, which may be normal but difficult to palpate on physical exam, warranting inguinal exploration. If the processus vaginalis is patent, the laparoscope can be advanced into the inguinal canal in most cases to again help identify the position and viability of the testis.

An intra-abdominal testis usually resides within a few centimeters of the internal ring and is most commonly associated with a patent processus vaginalis, potentially allowing the vas deferens to loop into the inguinal canal. While they are usually close to the internal ring, an intra-abdominal testis can be located anywhere along the path of descent and has also been reported ectopically in perinephric, perihepatic, and crossed ectopic locations. In cases where an intra-abdominal testis is not easily visualized, tracing the spermatic vessels from their origin will usually lead to the testis. Visualization of the spermatic vessels is facilitated by placing the child in the Trendelenburg position and laterally rotating the table to allow the intestines to fall away, exposing the psoas muscle. Rarely, the left colon or cecum may hide the testis, in which case another port can be placed in the contralateral lower abdominal quadrant for laparoscopic dissection. Inspection of the ipsilateral internal ring during diagnostic laparoscopy is also an important step. In 91% of boys with a patent processus vaginalis, the testis will be viable, whereas if the processus is closed, 97% of the testis will be vanished or absent.[33]

Once located, treatment options for an intra-abdominal testis include an orchiectomy (for a nubbin, extreme ectopic, or intra-abdominal testis in an older child with a normal contralateral gonad), primary laparoscopic orchiopexy, and primary or staged laparoscopic Fowler–Stephens orchiopexy. Choosing the appropriate procedure is based on the testis distance from the internal inguinal ring, the perceived redundancy of the vessels beneath the peritoneum, and the size of the child.

Primary Laparoscopic Orchiopexy

The initial dissection begins with taking down the distal attachments sharply at the internal ring which allows for



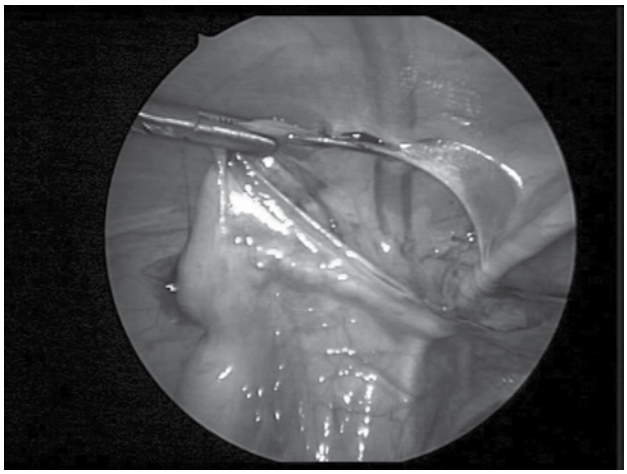


FIGURE 80.15 A left intra-abdominal testicle at the internal ring. The dark lines represent where peritoneotomies are made parallel to the testicular vessels (lateral) and vas deferens (medial) in order to mobilize the testicle on a vascularized peritoneal pedicle flap. The insert shows the same landmarks when an nonpalpable intra-canicular testicle is milked into the abdomen and then mobilized.

identification and eversion of intracanalicular contents (i.e. long looping vas) prior to dissection of the anterior peritoneum. Sharp dissection begins with a peritoneal incision at the internal ring made well lateral to the spermatic vessels, which is carried along the abdominal sidewall parallel to the psoas muscle and cranial toward the origin of the vessels. The second line of dissection is started at the internal ring medial to the vas and carried in a caudad direction following the course of the vas along the pelvic sidewall toward the bladder (Figure 80.15). These two incisions preserve a triangular wedge of peritoneum between the spermatic vessels and vas deferens, with the testis at the apex. It is sometimes necessary to isolate the window of peritoneum between these structures by incising the proximal peritoneum perpendicular to the vessels in order to gain more length. Even after this maneuver, if a single-stage Fowler–Stephens orchidopexy is the intended or possible procedure, the peritoneum between the spermatic vessels and vas has been preserved to prevent disruption to the collateral vasculature. This swath of peritoneum, which includes the vas and vessels, is mobilized away from the posterior retroperitoneum until sufficient length is gained that the testis can be brought to the contralateral internal ring without tension. It is often helpful at this juncture to use a radially dilating trocar introduced over a 2 or 3 mm instrument passed antegrade through the scrotum as an extra port to provide traction, as well as creating the eventual neocanal.[46]

Transferring the testis into the scrotum may be achieved by passing a curved hemostat from the subdartos pouch over the symphysis pubis into the peritoneal cavity if a trocar is not used to create the neocanal. If the antegrade technique is used, a 2–3 mm instrument is passed medial to the epigastric vessels and guided over the top of the pubis through the previously created dartos pouch. This instrument is then used to guide a radially dilating trocar sheath into the abdominal cavity, which is dilated to 5 or 10 mm (depending on the size of the testicle). Once the port has been placed, a locking grasper is used to grasp the gubernacular tissue distal to the testicle and deliver it to the scrotum (Figure 80.16). Regardless of the approach, it is critical for the surgeon to personally monitor the tension on the spermatic cord as the testis is passed into the scrotum to avoid avulsion of the spermatic vessels. While applying distal traction to the testis through the scrotum, further mobilization of the spermatic vessels may be obtained by dissecting the proximal peritoneum away from the spermatic vessels, and carrying the dissection of the spermatic vessels more cephalad toward the kidney. Care must be taken to avoid excessive traction and vascular avulsion as dissection is carried toward the origin of the vessels. Once sufficient length has been gained on the spermatic vessels, the testis is secured in the dartos pouch, as previously described. When there is slight tension on the spermatic cord, placement of an external nylon fixation button for 5–7 days is useful for protecting the testicular position in the scrotum.

Prior to port removal, bleeding should be assessed laparoscopically under low intra-abdominal pressure by releasing the pneumoperitoneum. Upon removing the ports, hemostasis should also be assessed at the port sites, as well as ensuring that the umbilical closure does not include bowel or omentum.

Laparoscopic Fowler–Stephens Orchidopexy

Determining if testicular vessels have sufficient length to allow for a tension-free orchiopexy does not need to be done early in the course of a laparoscopic orchidopexy as long as the distal peritoneal triangle is preserved. This is why laparoscopy is an ideal approach if the operator desires to preserve the spermatic vessels, if at all possible. On the other hand, there is evidence, although controversial, that primary Fowler–Stephens laparoscopic orchiopexies have lower success than staged procedures, so if it is highly likely that vessel division will be required, staging may be preferred. There are no absolute criteria that predict when division of the spermatic vessels will be required, but as a general guideline, a testis within 2 cm of the internal ring can usually be brought down without

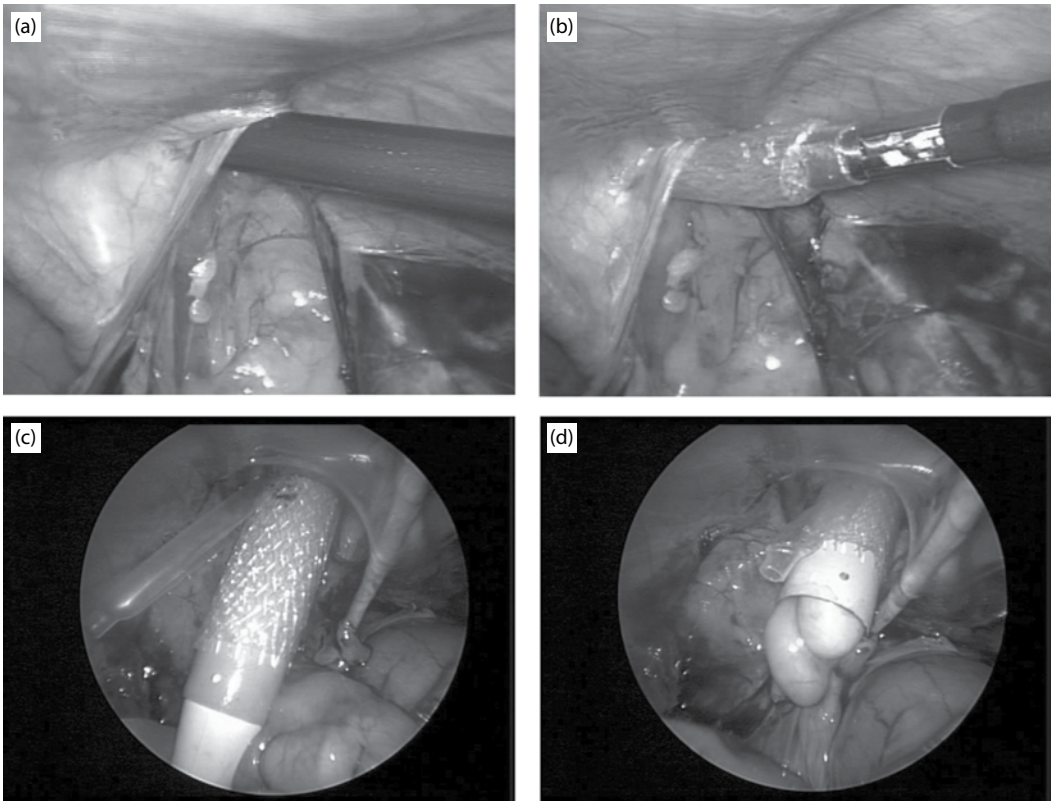


FIGURE 80.16 Delivering the testicle into the scrotum requires developing a neo-hiatus (a–c) to facilitate passage of the testicle, epididymis and cord structures into the scrotum without resistance. This technique minimizes the risk of an avulsion injury (d).

vessel transection, 2–4 cm from the ring may be possible with redundant vessels and vas, and 4 cm and beyond will likely require division of the vessels. Once the determination has been made to perform a staged procedure, vessel ablation is accomplished with surgical clips or a dissection device, such as the harmonic scalpel placed through a contra lateral 5 mm port.

The second stage of the orchidopexy is usually performed 6–9 months later, following principles similar to those of a first-stage procedure. If the vessels were clipped, the procedure begins by dividing the vessels. The gubernaculum can be divided or left intact, depending on whether the native canal or a more medial neocanal is going to be used. A wide peritoneal pedicle is developed by incising the peritoneum on either side of the vas deferens. The wide pedicle of peritoneum is carefully preserved to protect the vasal artery and collateral vasculature that has developed since division of the vessels. The testicle is then delivered into the scrotum and placed into a subdartos pouch as described above for a primary laparoscopic orchiopexy.

Microvascular Autotransplantation

At limited centers with microvascular surgical expertise, microvascular autotransplantation may be utilized in the management of high intra-abdominal testis. The results of testicular autotransplantation in uncontrolled studies appear to be superior to the predicted results reported with division of the spermatic vessels for the high intra-abdominal testis with both laparoscopic-assisted and open approaches.[47–49] Despite the reported success rate, outcomes are heavily dependent on microvascular expertise, which most likely accounts for why this approach has not been more widely adopted. When used, the technique is generally restricted to relocating a high, solitary testis.

Reoperative Orchiopexy

Reoperative orchiopexy is performed in cases of secondary cryptorchism after orchiopexy or inguinal hernia repair. Testes that are at risk for iatrogenic ascent after a hernia repair may be trapped in inguinal scar tissue, or may be ectopic, sitting in a low-lying superficial inguinal pouch or in a retroscrotal plane just beyond the confines of the anatomic scrotum, and at risk for testicular ascent even before inguinal surgery.

For an inguinal approach, the skin incision should be in a previously nonoperated area in order to identify landmarks and to allow approach of the inferior pole of the testis, progressing from normal to scar tissue. After the testis is freed, attention is turned to the spermatic cord, which is often densely adhered to the undersurface of the external oblique fascia. To lessen the risk of injury to the spermatic vessels, dissection lateral and medial to the cord in more normal tissues is performed, and in some cases, it is beneficial to leave a strip of fascia overlying the cord during the initial mobilization. It may also be necessary to mobilize the cord proximally above the internal ring in order to gain length in a now relatively inelastic cord. The usual surgical principles of a standard orchiopexy can then be applied, including positioning the cord more medially if required.

A more contemporary approach to reoperative orchidopexy is through a single scrotal incision.[50] The approach is similar to that of primary scrotal orchidopexy, except that the testis and cord are serially freed from surrounding scar tissue, releasing intrinsic elasticity and, in almost all cases, creating adequate length for scrotal location without the need for proximal dissection. This is our preferred approach to almost all orchiopexies after prior inguinal surgery.

Complications of Orchiopexy

As discussed in previous chapters, laparoscopic procedures are associated with unique risks, which include injuries associated with positioning, gaining access to the abdominal cavity, and intraperitoneal insufflation. Immediate complications that are unique to orchiopexy are avulsion of the testicular vessels, injury to the vas deferens, and damage to the bladder and surrounding vasculature. Testicular atrophy and suprascrotal position are the two major long-term complications with recurrence of inguinal hernia as a less common possibility.

Immediate Complications

Immediate complications of laparoscopic procedures can be avoided with proper positioning and using an open technique to gain peritoneal access.[51] During testicular mobilization, care must be taken to avoid injury to the vas; testicular, femoral, and iliac vessels; and the ureter. Using a gubernacular attachment as a handle, minimizing testicular manipulation, and preserving collateral blood flow between the vessels and the vas are all key steps in preventing immediate injury and long-term atrophy.[52,53] Avulsion of the spermatic vessels due to excessive traction placed on the testicle has been reported.[52,54,55] If the vessels are unintentionally injured, immediate conversion to a Fowler–Stephens orchiopexy may be possible. Injury to the bladder is most likely to occur when creating the neoinguinal hiatus. The risk is increased if the neohiatus is not formed superior to the pubis in a plane lateral to the medial umbilical ligament and medial or lateral to the epigastric vessels. Remaining cognizant of these pelvic landmarks is essential in preventing injury to the bladder or epigastric or femoral vessels.[56] Antegrade passage of the laparoscopic instrument to form the neocanal can be performed while palpating the tip with the receiving finger anterior to the pubis, further decreasing the likelihood of injury. Placement of a urinary catheter to maintain a decompressed bladder will also help to prevent bladder injury and may also serve to alert the physician of an injury to the bladder if grossly bloody urine is detected in the drainage bag.

Torsion of the testicular vessels to the scrotum following delivery has been reported.[57] This complication may be avoided by thoroughly examining the vessels after placement of the testicle into the scrotum to confirm the absence of torsion. If torsion is identified, the testicle is carefully repositioned in the scrotum until the vessels and vasa have a normal interrelationship.

When performing laparoscopic orchiopexy, the associated hernia sac is not ligated and the internal ring is generally not formally closed.[58] However, Metwalli and Cheng describe an indirect inguinal hernia following laparoscopic orchiopexy. In their series, this complication has occurred in 1 of 25 procedures, or 4%, although inguinal hernia after laparoscopic orchidopexy has not been reported in most large series. While they do not advocate for closure of the internal ring in all cases, they suggest that this may be appropriate in select cases where a large internal ring defect is evident.[59] Considering that this is the only reported inguinal hernia after laparoscopic orchiopexy, the risk appears to be well under 1% overall.

Long-Term Outcomes

For open procedures, Docimo reported a significant advantage to maintaining intact spermatic vessels in a retrospective literature review.[60] For primary laparoscopic orchiopexy, contemporary series have reported an overall success ranging from 82% to 100%, atrophy ranging from 2% to 4%, and persistent high testicular position in 0.6%–18%.[49,56,58,61] Overall success with laparoscopic single-stage Fowler–Stephens ranged from 71% to 97%, with 3%–22% atrophy and 0%–7% high testicular position.[46,52,62] As expected, laparoscopic two-stage Fowler–Stephens reported higher overall success rates (88%–96%) and lower rates of atrophy (4%–15%) when compared with single-stage procedures.[52,56,58] The only multi-institutional analysis, including 263 testes, demonstrated 97% success for primary laparoscopic orchidopexy preserving the vessels, 74% success with single-stage Fowler–Stephens laparoscopic orchidopexy, and 88% success with staged Fowler–Stephens orchiopexies.[58] Therefore, both historically and in a contemporary series, there is an advantage to maintaining vessels when possible, and staging procedures when vessels cannot be maintained.

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CHAPTER
81

Testicular and Paratesticular Tumors in Children

Lynn L. Woo and Jonathan H. Ross

INTRODUCTION

Prepubertal testis tumors are less common than other pediatric urological malignancies, such as neuroblastoma or Wilms' tumor, and testicular tumors occur less often in children than adults. Historically, management of pediatric testis tumors has been based on experience in adults; indeed, testicular tumors in both adult and pediatric patients share several common features, including presentation with a painless testicular mass that is initially treated with excision of the primary tumor. In both children and adults, testis tumors are very sensitive to platinum-based chemotherapy, which has revolutionized the management of testicular cancer throughout the age spectrum.[1,2] There are, however, important differences between testis tumors occurring in children and adults, which include tumor histopathology, malignant potential, and pattern of metastatic spread. The patients themselves are also dissimilar, with different concerns regarding surgical morbidity and preservation of testicular function. The introduction of the Prepubertal Testis Tumor Registry by the Urological Section of the American Academy of Pediatrics in 1980 allowed for the accrual of valuable epidemiological information.[3] Recent multicenter and prospective clinical trials have further advanced our understanding of these tumors and their management.[4–6]

EPIDEMIOLOGY

There is a bimodal age distribution for testis tumors, with one peak occurring in the first 3 years of life, and a second larger peak occurring in young adulthood.[7,8] The incidence of pediatric testis tumors is 0.5–2.0 per 100,000 children, accounting for 1%–2% of all pediatric tumors.[9–11] Testis tumors are categorized, based on the presumed cell of origin, into stromal tumors and germ cell tumors. In the Prepubertal Testis Tumor Registry of the Urological Section of the American Academy of Pediatrics, the majority of primary testis tumors were yolk sac tumors, followed by teratomas and stromal tumors.[3] A more recent review of the Surveillance, Epidemiology and End Results (SEER) database by Alanee and Shukla also found yolk sac tumor to be the most commonly observed pediatric testis tumor, at 43.5%.[12] Selection bias and underreporting have likely led to an overrepresentation of malignant tumors in registries, however, and several other studies have documented a predominance of benign testis lesions in children.[7,13–15] Indeed, a recent multicenter report found that benign lesions accounted for the majority of primary testis tumors (74%), with teratoma being the most common histological subtype (48%). Yolk sac tumors constituted only 15% of testicular neoplasms in this series.[14] Table 81.1 summarizes the distribution of testis tumors in the Prepubertal Testis Tumor Registry and a multicenter review of prepubertal testicular tumor pathology specimens. Because teratomas and most stromal tumors are benign in children, the percentage of prepubertal testis tumors that have malignant potential is much lower than the 90% of tumors in adults.

Based on the SEER database, authors reported no apparent increase in the incidence rate of testicular tumors in children of ≤14 years old since 1973, and 5-year relative survival rates were 97% for those with localized disease versus 73% for those with distant disease. Interestingly, for children under the age of 15, patients entered as American Indian, Alaskan native, Asian, or Pacific Islanders were most affected by yolk sac tumors, with an incidence rate twice that of Caucasians and eight times that of African American children.[12] The most common testicular malignancies in postpubertal patients are embryonal and mixed germ cell tumors.

EVALUATION

The majority of prepubertal patients with a testicular tumor will present with a painless, firm testicular mass noted by the patient, a parent, or a healthcare provider.[13] Occasionally, patients may present with diffuse testicular enlargement, a hydrocele, or pain secondary to torsion or bleeding into the tumor. Patients with hormonally active stromal-based tumors may exhibit gynecomastia, virilization, or precocious puberty.[16,17] Physical examination can usually distinguish testicular tumors from other scrotal masses, such as hydroceles, hernias, or epididymal cysts. Scrotal ultrasonography is a routine part of the evaluation and assists in both distinguishing extratesticular masses from those within the testis and characterizing tumor architecture. While ultrasound cannot reliably distinguish malignant from benign testicular tumors, hypovascular,

TABLE 81.1 Distribution of tumor types in the 395 primary testis tumors registered in the prepubertal testis tumor registry and 98 tumors in a multicenter consecutive series of patients

Tumor type		Percent of tumors in registry	Percent of tumors in multicenter study
Germ cell	Yolk sac	62	15
	Teratoma/epidermoid cyst	26	62
Stromal	Leydig cell	1	4
	Sertoli cell	3	3
	Juvenile granulosa cell	3	5
	Unspecified stromal	4	1
Gonadoblastoma		1	2

Source: Ross JH et al. *J Urol* 2002;168(4 Pt 2):1675–8; discussion 1678–9; Alanee S, Shukla A. *BJU Int* 2009;104(9):1280–3.

well-demarcated, or cystic tumors are more likely to be benign in children.[18,19]

Tumor markers typically utilized in the evaluation and management of adult testis tumors include human chorionic gonadotropin (HCG) and α-fetoprotein (AFP). While HCG is elaborated in a significant number of mixed germ cell tumors, this tumor type is vanishingly rare in prepubertal patients; therefore, HCG is not a useful marker for this population.[7] On the other hand, AFP is elevated in 90% of patients with yolk sac tumor and is an important marker to distinguish between yolk sac and other tumors (almost all of which are benign). One caveat is that AFP levels are normally high in infancy. However, AFP may be variable in infants; typical levels range from approximately 50,000 ng/mL in newborns to 10,000 ng/mL by 2 weeks of age, 300 ng/mL by 2 months, and 12 ng/mL by 6 months of age.[20] Therefore, AFP levels in patients with yolk sac tumors and benign tumors overlap in the first 6 months of life, making AFP a less helpful tool in distinguishing tumor types in young infants (Figure 81.1).[21]

Since many, if not most, prepubertal patients will have a benign tumor, the metastatic evaluation may be deferred until a histological diagnosis of the primary tumor is obtained. A preoperative metastatic evaluation may be undertaken in patients over 6 months of age with an elevated AFP level, who likely harbor a yolk sac tumor. Metastases from yolk sac tumor typically occur in the lungs and the retroperitoneal lymph nodes. A chest x-ray or chest computerized tomography (CT) scan and abdominal CT should be obtained. Postoperative AFP levels are also followed. The half-life of AFP is approximately 5 days, and failure of an elevated AFP to decline as expected following removal of the primary tumor is evidence of persistent metastatic disease.

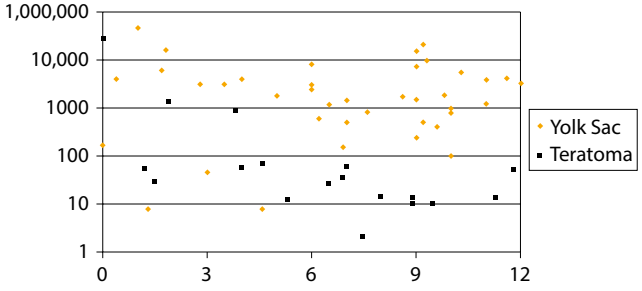

FIGURE 81.1 AFP level (ng/mL) as a function of age (months) for infants with a yolk sac tumor in the Prepubertal Testis Tumor Registry of the Urological Section of the American Academy of Pediatrics. (From Ross JH et al. *J Urol* 2002;168(4 Pt 2):1675–8; discussion 1678–9. Reprinted with permission.)

SURGICAL MANAGEMENT

The initial surgical approach in all patients with a suspicious testicular or paratesticular mass should involve an inguinal incision with early vascular control of the spermatic cord using a vessel loop or Penrose drain. The testicle is then delivered through the inguinal incision. Failure to follow these guidelines, particularly scrotal violation, may increase the recurrence rate in the setting of malignant tumor.[22] In prepubertal patients older than 6 months of age with an elevated AFP, and in most adolescents, radical orchiectomy should be performed.[3] In all other patients, a benign tumor is likely to be present, and testicular preservation will be the preferred goal. Following delivery of the testis, the tunica vaginalis is incised to expose it (Figure 81.2). Lesions involving or immediately adjacent to the tunica albuginea can be circumscribed beyond the tumor margins by making an elliptical incision in the tunica. Deeper lesions can be accessed through an equatorial incision in the testis, while intraoperative sonography has been recommended to localize impalpable lesions, similar to that reported in the adult literature.[23] Intraoperative frozen section has been shown to correlate well with final pathology and plays a key role in decision making.[24] If frozen section reveals a likely malignancy, then the entire testis and spermatic cord up to the internal inguinal ring are removed. If a benign histology is confirmed (usually teratoma), vascular control of the spermatic cord is released, and the remaining testis is closed by reapproximating the tunica albuginea with a running absorbable monofilament suture. The testicle is then returned to the scrotum. Even large tumors can be enucleated with preservation of significant testicular tissue (Figure 81.3).

One concern with this approach is the malignant potential of the remnant testicular tissue. In adults, 88% of testicles with teratoma harbor carcinoma in situ (CIS) elsewhere in the testis; therefore, radical orchiectomy is still an appropriate management in postpubertal patients.[25] However, in studies of prepubertal teratoma, with the exception of one case, no such finding has been evident.[19,26,27] Rushton et al. reviewed the histopathology of 17 prepubertal testes removed for teratoma, and no multifocal tumor or CIS was found in any specimen.[26] In initial small series of testis-sparing surgery for prepubertal benign tumors, there have been no cases of recurrent tumor in the preserved testicular remnant.[19,26,28–30] In 1999, Sugita et al. reported on 27 patients with teratoma, 17 of whom were treated with partial orchiectomy. With a mean follow-up of 10 years, there were no recurrences

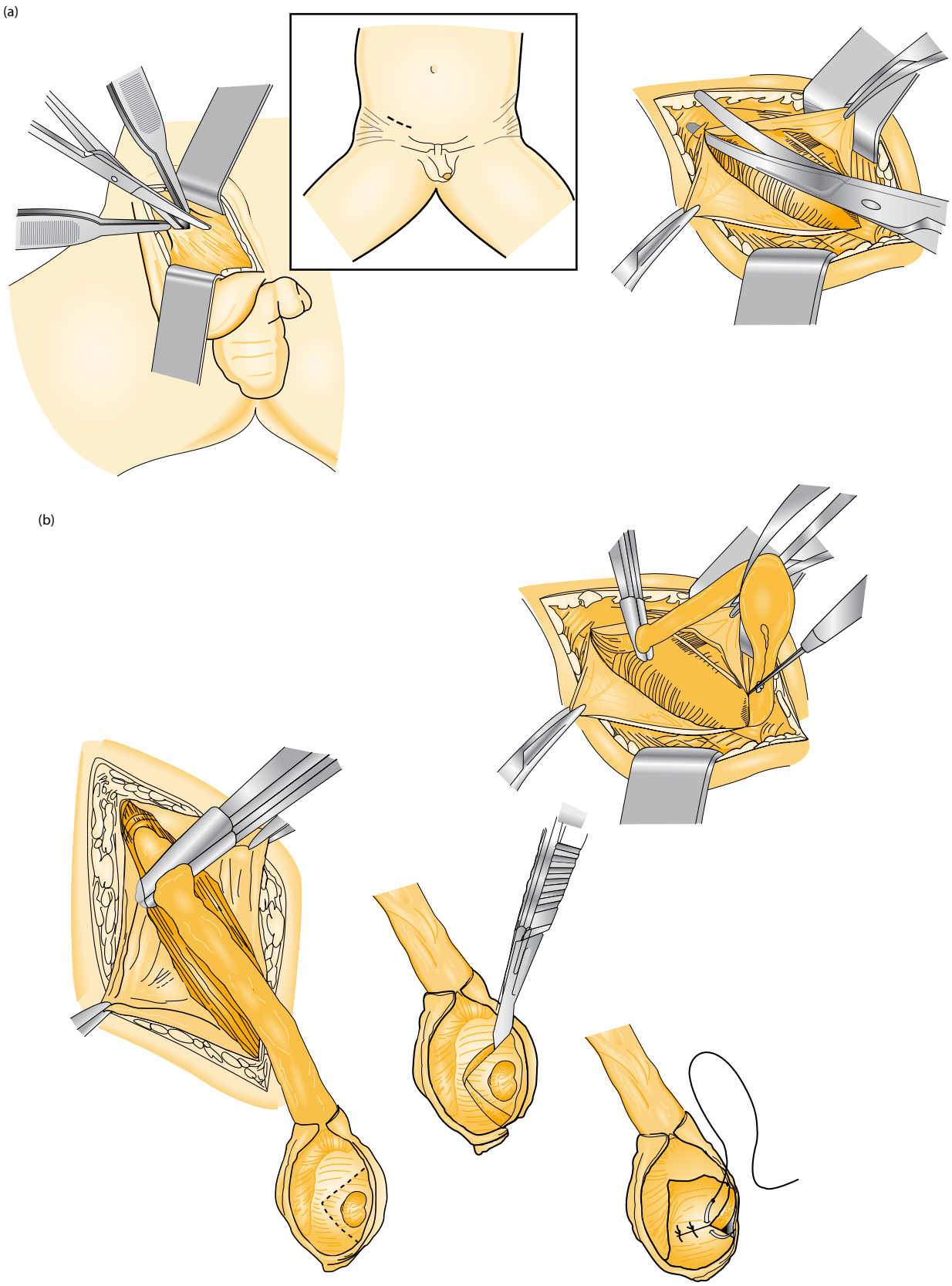

FIGURE 81.2 Inguinal exploration with testis-sparing tumor excision. (a) An inguinal incision is made and Scarpa's fascia is opened exposing the external oblique aponeurosis. This is opened along the length of its fibers through the external ring, exposing the spermatic cord structures. (b) The vessels are temporarily occluded and the testis delivered into the operative field. The hydrocele sac is opened and the tumor sharply excised. If a benign tumor is confirmed on frozen section, then the remnant testis is closed and returned to the scrotum.

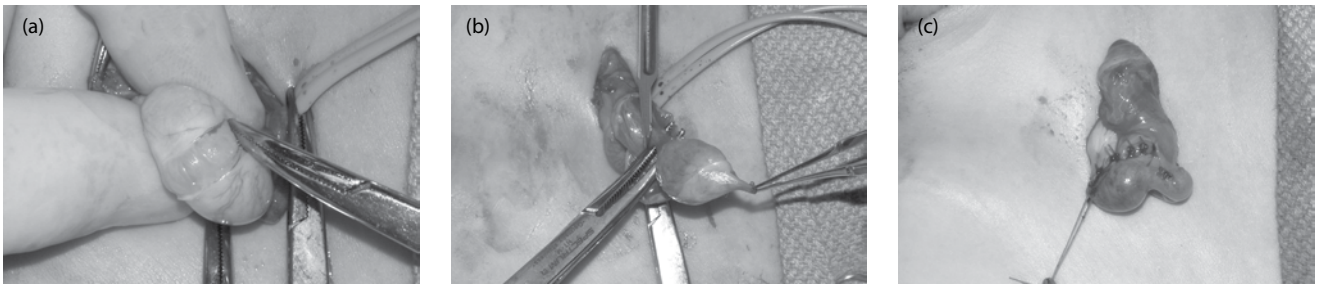

FIGURE 81.3 Enucleation of a benign tumor. (a) With the vessels occluded, an incision is made in the testicular tunix, exposing the cystic tumor. (b) The tumor is enucleated and detached from the testis. (c) The testis is closed with interrupted suture.

and no cases of testicular atrophy.[29] In these studies, testes undergoing testis-sparing tumor excision appear to maintain normal testicular volume postoperatively.

ADJUVANT THERAPY FOR MALIGNANT TESTICULAR TUMORS

There are little data regarding the behavior of mixed germ cell tumors in adolescents, although they appear to exhibit behavior similar to that seen in adults.[31] It is therefore assumed that they should be managed as in adults, with observation, retroperitoneal lymph node dissection (RPLND), and/or chemotherapy, depending on the specific histology and stage of the disease. This seems a reasonable approach until further studies in adolescents with testicular malignancies are undertaken.

Virtually all malignant germ cell tumors in children are yolk sac tumors. A yolk sac tumor is a yellow to pale gray solid tumor. It has been referred to by a variety of other names, including endodermal sinus tumor, orchioblastoma, juvenile embryonal carcinoma, mesoblastoma vitellinum, clear cell adenocarcinoma, extraembryonal mesoblastoma, and archenteronoma.[10] A variety of histological patterns may occur. Positive staining with AFP supports the diagnosis of yolk sac tumor. Classic glomeruloid (Schiller–Duval) bodies and embryoid bodies may be present. These structures are clusters of cells resembling the structures for which they are named (Figure 81.4).

As with most malignancies, adjuvant therapy for yolk sac tumor is based on tumor stage. Different cancer study groups employ different staging systems. However, detailed staging is unnecessary since the number of patients with metastatic testis tumors in all series is very small, and stratifying response rates and tumor behavior based on the extent of metastatic disease is impossible. Indeed, in large studies all metastatic yolk sac tumors are treated the same, regardless of the extent or location of metastatic disease. Therefore, the important distinction for yolk sac tumors is between Stage 1 disease (disease limited to the testis and completely excised) and those tumors with any degree of residual or metastatic disease.

The majority of prepubertal testis tumors present with Stage 1 disease.[3] Recent studies suggest that these patients can be safely managed with observation, followed by chemotherapy for patients in which tumors recur.[4–6,32–34] The United Kingdom Children's Cancer Study Group, the German Society of Pediatric Oncology, and the U.S. Pediatric Intergroup Study (now the Children's Oncology Group) have reported their results employing observation for Stage 1 yolk sac tumor of the testis and platinum-based

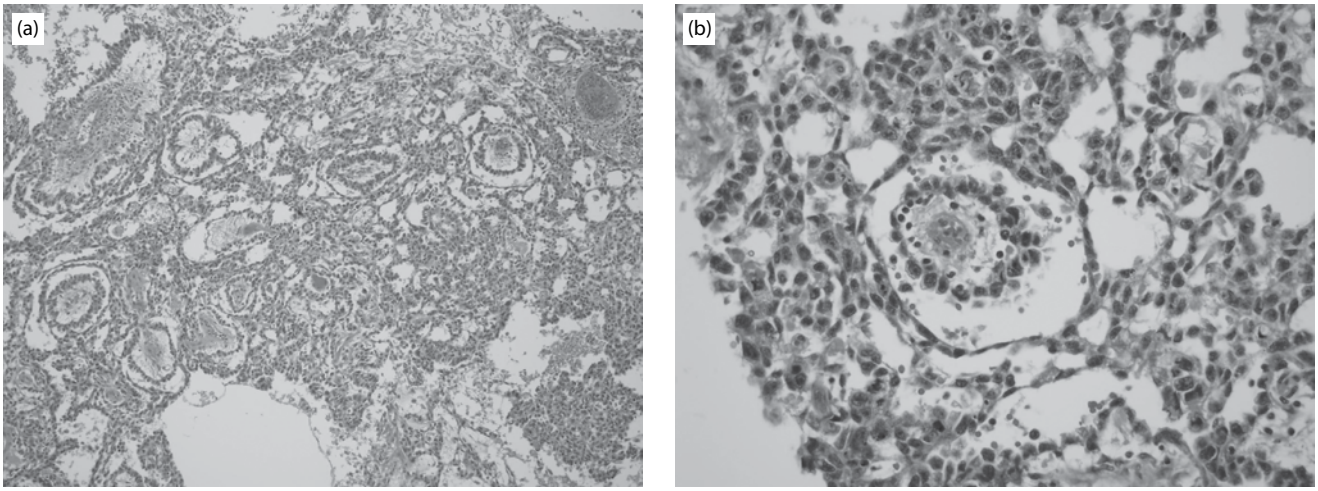

FIGURE 81.4 Yolk sac tumor. (a) The endodermal sinus pattern of yolk sac tumor is characterized by irregular interconnecting labyrinth-like spaces admixed with Schiller–Duval bodies, several of which are readily apparent in this image. (b) Schiller–Duval bodies are pathognomic features of yolk sac tumors and are composed of a fibrovascular papillary structure lined by malignant cells, encircled within a small cystic space that is also lined by flattened malignant cells.

TABLE 81.2 Results of three large multicenter studies of pediatric testicular yolk sac tumors

	Number of patients	Percent with stage 1 tumors	Recurrence rate (%) of stage 1 tumors on observation	Chemotherapy for recurrent or metastatic disease	Percent survival for stage 1 tumors	Percent survival for those with residual disease/ metastases
United Kingdom Children's Cancer Study Group[20]	73	70	22	Bleomycin, etoposide, carboplatin	100	100
German Cooperative Studies[21]	110	95	15	Bleomycin, vinblastine, cis-platinum	100	80
U.S. Pediatric Intergroup Study[22]	79	82	18	Bleomycin, etoposide, cis-platinum	100	100
Total	262	84	17		100	98

chemotherapy for patients with recurrent or metastatic disease. Most patients with recurrent or metastatic disease received four cycles of chemotherapy. The potential toxicities of the chemotherapy regimens employed include myelosuppression, ototoxicity, and renal toxicity from platinum-based agents and pulmonary toxicity from bleomycin. High-grade ototoxicity was rare in the UK study, which utilized carboplatinum rather than cis-platinum. However, carboplatin is more myelotoxic.[4–6]

A summary of the three large multicenter studies is presented in Table 81.2. Eighty-four percent of all patients presented with Stage 1 disease. Overall, the recurrence rate for patients with Stage 1 tumors managed with observation was 17%, and all were cured with chemotherapy. The overall survival of all patients receiving chemotherapy for recurrent or metastatic disease was 98%. Clearly, the outlook for prepubertal testis tumors is excellent. Stage 1 tumors are best managed with orchiectomy and observation. Observation should include frequent chest and abdominal imaging and measurement of AFP levels. Patients with recurrent disease or metastatic disease can expect excellent results with platinum-based multiagent chemotherapy. Future studies will focus on reducing the morbidity for those patients requiring chemotherapy by reducing the number of agents and/or cycles of therapy administered.

Another shift in the management of prepubertal testis tumors has been away from the performance of RPLND, once a standard component of management.[35–37] The rationale for this dissection in select adolescent and adult patients is the likelihood of retroperitoneal disease and the ability to avoid the morbidity of chemotherapy in some patients. Several characteristics of prepubertal tumors argue against its use in children. Most prepubertal patients have clinical Stage 1 disease, and the recurrence rate for these patients with observation alone is only 17%. Nearly all the recurrences can be salvaged with chemotherapy. For those with metastatic disease, it appears that only a minority of prepubertal patients have disease limited to the retroperitoneum.[38] The majority have disease in the chest (with or without retroperitoneal disease). Finally, the morbidity of abdominal surgery is greater for children than for adults. Children have a particularly high rate of postoperative bowel obstruction. It is also unclear that a nerve-sparing approach is technically feasible in small children. For prepubertal testis tumors, RPLND is limited to patients with persistent retroperitoneal masses following chemotherapy—a rare occurrence.

SCROTAL VIOLATION

Scrotal violation by means of scrotal orchiectomy, needle biopsy, or tumor spillage has long been condemned in the surgical management of malignant testicular and paratesticular masses given the theoretic alteration of lymphatic drainage and increased risk of tumor recurrence, both locally and systemically.[39] Prior orchidopexy has also been considered a form of scrotal violation by some authors. Published studies are small in number and limited primarily to the adult population. In these instances, additional treatment has been advocated, including hemiscrotectomy or wide excision of the scrotal scar and removal of the cord remnant through a separate inguinal incision.[40] Similarly, in the case of paratesticular rhabdomyosarcoma, scrotal violation has been managed with hemiscotectomy and/or more intensive chemotherapy, as well as scrotal irradiation.[41] Several groups have questioned the need for adjuvant surgical procedures, however, citing increased morbidity and disfigurement. A meta-analysis of all published series of testicular cancer patients with scrotal violation revealed a small but significant increase in the local recurrence rate (2.9% vs. 0.4%) but no overall increase in the distant recurrence or survival rates. Furthermore, patients with scrotal violation who did not receive local therapy had outcomes similar to those who had.[42] A review by the Children's Cancer Group/Pediatric Oncology Group of 63 patients with Stage 1 testicular germ cell tumors found no statistical significance in event-free survival between those who underwent the correct surgical approach and those who had surgical violations, although 4 patients with scrotal violation did have a higher incidence of disease recurrence.[22] For scrotal violation in the setting of paratesticular rhabdomyosarcoma, Dall'Igna et al. proposed primary reexcision as a nonmutilating alternative to hemiscrotectomy. It is worth noting, however, that eight patients in this series, who did not undergo primary reexcision as recommended, were alive without recurrence at a median of 170 months. Interestingly, this group of eight patients were all prepubertal, between age 2 and 5 years, possibly reflecting the favorable prognosis of younger patients with paratesticular rhabdomyosarcoma.[41]

TERATOMA AND EPIDERMOID CYST

Teratoma is the most common benign tumor in prepubertal patients, ranging from 8% to 48% in various series.[3,12,14] The median age of presentation is 13 months, although there have been several reports of patients presenting in the neonatal period.[21,43] Histologically, teratomas consist of tissues representing the three germinal layers: endoderm, mesoderm, and ectoderm. Consequently, cartilage, fat, bone, muscle, and neural elements may be seen in the specimen. Ultrasound may demonstrate a heterogeneous mass, reflecting cystic and solid components, with internal calcifications.[44] The findings of diploid DNA content with an absence of cellular atypia or widespread mitotic activity are characteristic.[45] AFP levels are not elevated in patients with pure teratoma.

Epidermoid cysts are benign tumors composed entirely of keratin-producing epithelium and are distinct from dermoid cysts, which contain skin and skin appendages, and teratomas, which contain derivatives of other germ cell layers. Both teratomas and epidermoid cysts are universally benign in prepubertal children. On ultrasound, most epidermoid cysts appear as discrete intratesticular masses with areas of increased echogenicity corresponding to the keratin debris or peripheral calcification.[46,47]

The benign nature of these tumors favors testis-sparing surgery.[48] At the time of inguinal exploration, an excisional biopsy with frozen section should be performed to confirm the diagnosis.[19,26] In older children with teratoma, surrounding testicular parenchyma should be carefully evaluated for histological evidence of pubertal changes. If present, then orchiectomy should be performed, given the malignant potential in postpubertal males. Biopsies of surrounding testicular parenchyma are probably unnecessary in prepubertal patients.[26,27,30] While 88% of testes removed for adult teratoma contain areas of intratubular germ cell neoplasia, this has generally not been the case for epidermoid cysts or for pediatric teratoma.[19,25–27]

For patients with epidermoid cyst and prepubertal patients with teratoma, no radiographic studies or follow-up for the development of metastatic disease are required. Because of the potential for malignancy, postpubertal patients with teratoma should be evaluated and followed on the same protocol as adults with potentially malignant germ cell tumors.

GONADAL STROMAL TUMORS

Stromal tumors include Leydig, Sertoli, and juvenile granulosa cell tumors, and mixed or undifferentiated tumors. They represent a rare and heterogenous group of neoplasms originating from nongerm cells, with differing biologic activity and clinical features.[49] Stromal testis tumors are very rare in children, and there are no large studies to guide their management. However, anecdotal reports and small series in the literature offer some experience on which to base therapy.[17,49] Leydig cell testis tumors usually present between 5 and 10 years of age with a painless testis mass and precocious puberty. Small series and case reports of unilateral lesions have documented the uniformly benign nature of these neoplasms in children, in contrast to the 10% of these tumors that are malignant in adults.[10,17] A single report of malignant bilateral Leydig cell tumors with pulmonary metastases and hemoptysis in a 9-year-old boy has been published, although it is unclear if true lung involvement by the tumor was pathologically confirmed.[50] Congenital adrenal hyperplasia (CAH) can also lead to precocious puberty and testicular masses and must therefore be excluded through laboratory evaluation. Patients with Leydig cell tumors typically have elevated testosterone levels with low or normal gonadotropin levels, whereas patients with CAH will usually have elevated levels of 17-hydroxyprogesterone. Because of their benign behavior in prepubertal children, Leydig cell tumors may be treated by testis-sparing excision.[51,52] Persistence of androgenic effects may be due to a contralateral tumor, but this is rare in children. Because Leydig cell tumors are sometimes difficult to detect on physical exam, ultrasound may be necessary to rule out a contralateral tumor. Even after successful removal of a solitary tumor, androgenic changes may not be completely reversible, and some children may proceed through premature puberty due to activation of the hypothalamic–pituitary–gonadal axis.

Sertoli cell tumors are also exceedingly rare in children. The median age of patients in the Prepubertal Testis Tumor Registry was 6 months, with a range of 4 months to 10 years.[17] Sertoli cell tumors are usually well circumscribed with a creamy, white lobulated appearance. Cysts are common. Microscopically, an interlacing network of loose fibrous stroma and parenchyma, composed of small cells with irregular hyperchromatic nuclei, is observed, which recapitulates the appearance of immature seminiferous tubules containing Sertoli cells.[53] Approximately 10% of adult Sertoli cell tumors are malignant. Sertoli cell tumors are usually hormonally inactive in children, although they may occasionally cause gynecomastia or precocious puberty secondary to estrogen or androgen elaboration. While all reported cases to date have been benign in children under 5 years of age, there have been a few cases of malignant Sertoli cell tumors in older children.[54,55] Orchiectomy is usually sufficient treatment in infants and young children. A metastatic evaluation could be considered in older children and in patients with worrisome histological findings, including vascular invasion, high mitotic index, and tumor necrosis.[17,55] When metastatic disease is present, aggressive combination treatment, including RPLND, chemotherapy, and radiation therapy (XRT), should be considered.

The large-cell calcifying Sertoli cell tumor is a clinically and histologically distinct entity with a higher incidence of multifocality and hormonal activity.[10,56–59] These tumors are composed of large cells with abundant cytoplasm and varying degrees of calcification, ranging from minimal amounts to massive deposits. While standard Sertoli cell tumors are more common in adults, large-cell calcifying Sertoli cell tumors are found predominantly in children and adolescents. Most present with a testicular mass. Approximately one-fourth of patients have bilateral and multifocal tumors. The presence of calcifications results in a characteristic ultrasound appearance, including multiple hyperechoic areas. Approximately one-third of patients with large-cell calcifying Sertoli cell tumor have an associated genetic syndrome and/or endocrine

abnormality. The two most commonly associated syndromes are Peutz–Jeghers syndrome, characterized by mucocutaneous pigmentation and hamartomatous intestinal polyposis, and Carney's syndrome, characterized by myxomas of the skin, soft tissues, and heart; myxoid changes of the breast; lentigines of the face and lips; cutaneous blue nevi; Cushing's syndrome; pituitary adenoma, and schwannoma.[60,61] Screening for these syndromes in patients with large-cell calcifying Sertoli cell tumors is important since the patients and their first-degree relatives are at risk for the potentially lethal associated anomalies. While occasionally malignant in adults, large-cell calcifying Sertoli cell tumors have been universally benign in patients under 25 years of age, and inguinal orchiectomy is sufficient treatment for children.

Juvenile granulosa cell tumor is a stromal tumor bearing a light microscopic resemblance to ovarian juvenile granulosa cell tumor. However, the histological origin of this tumor in testicles is unclear. Granulosa cell tumors occur almost exclusively in the first year of life, most in the first 6 months. Of 22 tumors diagnosed in newborns in the Prepubertal Testis Tumor Registry, 6 were juvenile granulosa cell tumors, 6 were yolk sac tumors, and 6 were unspecified stromal tumors.[43] Structural abnormalities of the Y chromosome and mosaicism are common in boys with juvenile granulosa cell tumor.[54] Several cases have been described in association with ambiguous genitalia.[62] These tumors are hormonally inactive and benign. Although these children should undergo chromosomal analysis, no treatment or metastatic evaluation is required beyond testis-sparing excision.[17,63]

Undifferentiated stromal tumors consist of areas of gonadal stromal neoplasia and undifferentiated regions of spindle cells that may exhibit a high mitotic rate. These stromal tumors have an epidemiology similar to that of granulosa cell tumors.[17] Although some of these tumors have histological characteristics commonly associated with malignancy, most behave in a benign fashion. There are inadequate data in the literature to formulate rigid guidelines for managing these tumors. While aggressive behavior has not occurred in young infants, there are reports of such behavior in older children. Unfortunately, histological features do not appear to correlate with invasive or metastatic potential. Since orchiectomy cures most of these patients, aggressive treatment is probably not appropriate in the absence of radiographic evidence of metastatic disease. However, given the uncertainty, postoperative evaluation and follow-up for the development of metastatic disease seems prudent for patients with this rare tumor.

GONADOBLASTOMA

Gonadoblastomas are benign tumors that typically arise in dysgenetic gonads. They contain both germ cell and stromal elements.[64] Dysgenetic or "streak" gonads are gonads that have failed to develop normally and contain fibrous tissue and primitive ovarian structures. If the gonad has features of primitive testicular development, it is usually referred to as a dysgenetic testis rather than a streak gonad. Gonadoblastoma arises almost exclusively in the dysgenetic gonads of patients with a Y chromosome or evidence of some Y chromatin in their karyotype. Dysgenetic gonads in patients without Y chromatin, such as patients with Turner's syndrome or XX gonadal dysgenesis, seem to be at little risk. Gonadoblastomas have been reported in 3% of true hermaphrodites, up to 15% of those with partial androgen insensitivity, and 10%–30% of patients with mixed gonadal dysgenesis or pure gonadal dysgenesis in the presence of Y chromatin.[65–67] They also occur commonly in dysgenetic testes.[68] While gonadoblastomas are benign, they are prone to malignant degeneration, and overt malignant behavior is seen in 10% of cases.[66] While most cases of malignancy occur after puberty, there have been cases reported in young children as well.[66] Therefore, early prophylactic removal of dysgenetic gonads is recommended. If malignant elements are present, a metastatic evaluation should be undertaken. Dysgerminoma (or seminoma) is the most common malignancy to occur in association with gonadoblastoma. Like their counterpart in normal testicles, these tumors are very radiosensitive, and the oncologic outlook for these patients is generally favorable.

TESTIS TUMORS IN CONGENITAL ADRENAL HYPERPLASIA

CAH in boys, most often secondary to 21-hydroxylase deficiency, typically presents with precocious puberty. Adrenal rests, which are commonly found along the spermatic cord and in the testicular hilum in normal, healthy patients, may hypertrophy in patients with CAH, leading to testicular nodules clinically indistinguishable from testicular tumors. These lesions are known as testicular adrenal rest tumors (TARTs) and may be associated with infertility in this subset of patients.[69] They can also be seen in other diseases with elevated adrenocorticotropic hormone (ACTH) levels, such as Nelson's syndrome or Cushing's disease.[70] The clinical picture can be confused with Leydig cell tumor, which can also cause precocious puberty. In patients with CAH, these nodules are often multifocal and bilateral. The diagnosis of CAH can generally be made by demonstrating an elevated serum 17-hydroxyprogesterone level. In this setting, TARTs will usually resolve or significantly decrease in size with steroid replacement. Appropriate decreases in their size after medical treatment can give an indication as to the adequacy of steroid management.[71–74] If appropriate regression is observed, the patient may be followed with serial examinations.[75] Any TART that fails to respond should be biopsied. Large nodules that fail to shrink may be safely enucleated, which can help maximize future fertility potential.[16,74,75]

LEUKEMIA

Historically, the urologist played an important role in the evaluation of patients with acute lymphoblastic leukemia (ALL) because of the concept that the testis was a site protected from therapy by the "blood–testis barrier." Approximately 20% of ALL patients have microscopic

involvement at diagnosis, and pretreatment biopsy was common.[76] Following treatment, biopsy was undertaken to detect the 10% of patients with persistent testicular disease. However, with current chemotherapy, most patients with microscopic testicular involvement achieve a complete remission. Conversely, some patients without histological evidence of testicular involvement at diagnosis will ultimately relapse in the testicles. Therefore, pretreatment testicular biopsy is no longer recommended since it does not predict those at risk for persistent or relapsing disease. Modern treatment has reduced the posttreatment relapse rate to less than 1%. Therefore, posttreatment biopsy in the absence of clinical evidence of persistent disease is also unnecessary.[77] Rare patients with persistent or recurrent testicular enlargement following chemotherapy should undergo testicular biopsy to confirm the presence of ALL. In most cases, the patient will have relapsed at other sites and further systemic treatment will be required. Typically, the testicles are also treated with radiation.

PARATESTICULAR MASSES

Paratesticular structures include the spermatic cord, epididymis, appendiceal remnants, and tunica vaginalis. Benign lesions (leiomyoma, fibroma, lipoma, and hemangioma) and malignant lesions, such as the corresponding sarcomas, can be seen across all age groups but are rarely reported in the prepubertal population, with the exception of paratesticular rhabdomyosarcomas.[78] Inguinal exploration, frozen section, and testicular sparing are recommended for benign extratesticular tumors of <3 cm in size, while inguinal orchiectomy remains the standard of care for malignant lesions.[10,79]

Paratesticular rhabdomyosarcomas account for approximately 7% of all rhabdomyosarcomas in children and are derived from mesenchymal elements of the paratesticular tissues.[80] Grossly, the cut surface has a white-gray color with areas of hemorrhage and cystic degeneration. Several histological patterns, including embryonal, pleomorphic, and alveolar, are described and correlate with tumor behavior and prognosis. Metastases occur most often to regional lymph nodes, lung, and/or bone.[81] Like primary testicular tumors in children, paratesticular rhabdomyosarcoma presents as a firm mass, with a bimodal age distribution of 3–4 months and the teenage years. Despite the highly malignant nature of these neoplasms, the majority of paratesticular rhabdomyosarcomas exhibit the more favorable embryonal histology, and overall 5-year survival exceeds 80% in several recent series. Several studies have demonstrated a poorer prognosis in boys older than 10 years, with alveolar histology, unresectable retroperitoneal disease, and/or distant metastases.[80,82–84] Management consists of radical inguinal orchiectomy with associated metastatic evaluation, including abdominal and chest CT, liver function tests, and bone scan. Based on classification according to pathologic group and stage, various combinations of chemotherapeutic agents, including vincristine, dactinomycin, cyclophosphamide or ifosfamide, and doxorubicin are administered. Likewise, disease classification dictates the need for XRT. Patients with completely resected, localized paratesticular rhabdomyosarcomas of embryonal histology do not require XRT; those with retroperitoneal involvement receive XRT. Staging ipsilateral RPLND is recommended in all boys older than 10 years, regardless of CT findings, followed by intensified radio- and chemotherapy with vincristine, dactinomycin, and cyclophosphamide in those with positive nodes.[83,85]

FERTILITY CONSIDERATIONS

Future fertility for children with cancer is increasingly being recognized as a major component of quality of life. Fertility preservation is among the goals of achieving good outcomes for cancer survivors and can be particularly challenging in prepubertal patients. Alkylating agents used in chemotherapy and radiation are toxic to male germ cells. While the prepubertal testis appears to be more resistant to injury than the postpubertal testis, oligozoospermia, which can sometimes be reversible, has been well described in patients who received combination chemotherapy as children.[86] A recent study of young males found that boys 0–4 years at age of treatment were more likely to sire a pregnancy than those who were 15–20 years old at the time.[87] Due to a slower rate of turnover, Leydig cells are less vulnerable than germ cells to the effects of chemotherapy and low-dose radiation, and while Leydig cell dysfunction may be observed following cancer treatment, most boys go on to have normal puberty with normal testosterone levels. The present options for actively retaining the reproductive capacity of young children undergoing cancer treatment remain experimental and include cryopreservation of spermatogonial stem cells, xenotransplantation, and in vitro maturation of spermatozoa.[88] For adolescent males undergoing treatment that can adversely affect fertility, sperm banking should be offered. This approach is underutilized despite the fact that Tanner 4 or 5 boys as young as 12 years old can successfully provide a usable sample. In one study, 86% of 238 boys 12–19 years old were successful at providing usable semen.[89]

CONCLUSION

Testicular tumors are rare in the prepubertal population, and the majority of these lesions are benign, with mature teratoma the most frequently observed pathology. Yolk sac tumor is the most common malignant testicular mass seen in children and usually presents with an elevated AFP. For testicular tumors occurring in prepubertal patients with normal AFP, testicular-sparing surgery should be considered. Favorable prognosis with excellent survival rates is typically observed. Adolescents present with tumors typically seen in adults and are generally managed in a similar fashion, although data specific to adolescent patients are lacking. Future goals in the management of pediatric testis tumors should be aimed at reducing the morbidity of treatment for patients with favorable disease, including strategies to limit the intensity of therapy, minimize radiation exposure during follow-up, and optimize preservation of fertility.

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CHAPTER 82

Tumors of the Retroperitoneum

Gordon A. McLorie and Guy Hidas

INTRODUCTION

Retroperitoneal tumors of nonrenal origin are relatively uncommon in children. The most significant are neuroblastoma, sacrococcygeal teratoma (SCT), the rare childhood pheochromocytoma, and adrenal carcinoma. This chapter focuses on these four tumor types, with primary emphasis on the first two. The listing given in Table 82.1 of nonrenal retroperitoneal tumors is included for completeness.

NEUROBLASTOMA

Neuroblastoma accounts for 8%–10% of all childhood cancers. Following the original description by Virchow in 1864, it has continued to capture the imagination and interest of pediatricians, surgeons, and scientists. Historic landmarks in the biology of neuroblastoma include the understanding of the relationship of this childhood malignancy to the secretion of neuroactive substances in 1957, followed by the ability to establish a biochemical diagnosis based on the urinary secretion of catecholamines. Cushing described its transition in biologic activity from a malignant tumor to one of a benign nature, while Beckwith and Perrin[1] noted that clusters of neuroblastic nodules resembling neuroblastoma in situ were an incidental finding in the adrenal glands in children dying of other diseases. These clues provided the initial impetus that led to the recognition of the now well-known phenomenon of spontaneous regression of some neuroblastomas. Newer advances in molecular research have provided significant further insight into the biology of neuroblastoma. Furthermore, the paradigms described for neuroblastoma have acted as a template for diagnostic staging and applications of molecular and genetic insights to clinical therapies of other childhood malignancies. Fingerprinting the tumor's molecular characteristics (beyond MYCN proto-oncogene expression) has allowed stratification of children with neuroblastoma into distinctive clinical subsets. These stratification and staging methodologies provide better applications of therapeutic options and appropriate balancing of therapies that are more aggressive to children with poor prognostic disease. They also allow us to pursue a goal of less aggressive therapies to be used for those children in whom better prognosis can be defined.[2]

Recent insights have unfolded as a result of neonatal screening programs in Japan and Canada. In these programs, the secretion of urinary vanillylmandelic acid (VMA) in the newborn has been used as a method of neuroblastoma detection. However, early detection has neither reduced the occurrence nor improved the prognosis of those children who are discovered to have higher-grade tumors in later infancy and childhood. This has led to the thesis that the tumors detected during neonatal screening programs are those that have a natural propensity for spontaneous resolution.[3,4] The results suggest that mass screening for neuroblastoma, while feasible, is unlikely to alter the course of those patients destined to succumb to the disease.

Clinical and Biological Features

Neuroblastoma ranks as the most common extracranial solid malignancy of childhood[5] and early infancy. The incidence may be increasing slightly.[5,6] In children presenting with neuroblastoma, 65% will occur in the retroperitoneum, of which 40% will originate in the adrenal gland.[7]

Few, if any, environmental risk factors have been identified for neuroblastoma. Recently, maternal vaginal infections, their treatment, and prenatal maternal hormone use have been weakly suggested to increase the risk of neuroblastoma in offspring.[8] Pesticide exposure has been suggested as being associated with an increased risk of carcinogenesis in children compared with adults; the risk included, but was not specific for, neuroblastoma.[9]

While newer molecular modalities are helping to refine prognostic groupings and treatment assignment, the overwhelming variables distinguishing high- from low-risk groups continue to be age at diagnosis, tumor stage, and histologic grade.[10] Diagnosis before 12 months of age is more clinically favorable than later diagnosis.

Any predisposition for neuroblastoma appears to follow an autosomal dominant pattern, as elucidated by the two-hit hypothesis of Knudson and Strong.[11] Also described for Wilms' tumor and pheochromocytoma, inherited forms of neuroblastoma may occur in patients who harbor a mutation in a gene that preexisted in a parental germ line (preconception or germinal mutation). A subsequent spontaneous mutation of the other copy of the same gene (a somatic mutation) in a cell of the appropriate background (neural crest cell) leads to malignant transformation of that cell. This has led to estimates that more than one-fifth of all neuroblastoma may be of the inherited variety.[11] The occurrence of nonfamilial neuroblastoma must therefore

TABLE 82.1 Nonrenal retroperitoneal tumors

Benign	Malignant
Lymphangioma	Neuroblastoma
Neurofibroma	Pheochromocytoma
Ganglioneuroma	Sacrococcygeal teratoma
Lipoma	Nongenitourinary pelvic
Sacrococcygeal teratoma	Rhabdomyosarcoma
	Lymphoma
	Liposarcoma
	Fibrosarcoma
	Leiomyosarcoma
	Malignant fibrous
	Histiocytoma
	Secondary tumors

await these two critical mutations or "hits" as two independent spontaneous events. This explains the reduced likelihood (incidence) of nonfamilial or sporadic disease. With one of two mutations possibly present in all cells of a given child with a strong family history of neuroblastoma, it is easy to see why earlier incidence, bilaterality and multifocality, and higher recurrence rates are the norm in those with familial disease. Exceptions to the two-hit hypothesis have been reported (familial neuroblastoma in older children), suggesting that other genetic mechanisms may also underlie familial disease.[12] While several reports exist of neuroblastoma being found in children with a chromosomal abnormality, few chromosomal predispositions have been definitively associated with neuroblastoma. Abnormal rearrangements have been described involving chromosomes 1 and 17 (see below). Deletions involving 1p36 have implicated this region as containing a neuroblastoma tumor suppressor gene, and gains in the 17q region have been associated with poor prognosis.[12–17] Finally, loss of heterozygosity (LOH), a molecular phenotype characterized by the loss of the subtle differences that normally exist between the two allelic (parental) copies of any gene signifying that one of the copies is missing, has been identified as a more general phenomenon in neuroblastoma. Subjects with LOH are therefore homozygous instead of heterozygous for that particular chromosomal region. When a disease becomes evident in association with LOH in particular regions of a chromosome, this implies that the missing region of that chromosome encodes a gene or genes responsible for suppressing that disease, i.e., tumor suppressor genes. Although LOH does not identify the missing gene itself, LOH in neuroblastoma has been reported present in a number of chromosomes, including 1p, 11q, 14q, 2q, 9p, and 18q.[18]

Clinical Manifestations: Primary, Metastatic, and Paraneoplastic Features

The presenting signs and symptoms are variable and may reflect the effects of the tumor, the presence of metastatic disease, or the results of tumor hormone production. As mentioned earlier, prenatal screening may also identify neuroblastoma. Infants may present with an abdominal mass that is often huge. A unique feature of neuroblastoma in children is the potential for widespread liver metastatic disease that may signify stage 4S disease (Figure 82.1).

Children with stage 4S have a potential survival rate of up to 90%, in spite of metastases to either the liver, skin, or bone marrow, but not to cortical bone. Subcutaneous nodules are another manifestation of this early presentation.[20] In some patients, tumors regress spontaneously. Alternatively, metastases may regress following excision of the primary tumor.[21,22] In children older than 1 year of age, the size of the abdominal mass is variable and may not be the presenting symptom. Malaise and/or pain reflecting the presence of metastatic disease is the presenting complaint in up to 60%. Anemia (from bone marrow involvement in 50% of patients) is also a common presenting sign. The new or sudden onset of constipation or urinary retention may herald the well-known propensity of neuroblastoma to invade the spinal cord. In addition, transient pain attributable to bony metastases may mimic rheumatoid arthritis. Lung or brain metastases are common sites of relapse and late-stage disease.

Paraneoplastic syndromes occur in fewer than 5% of neuroblastoma patients. Intractable diarrhea may result from the secretion of vasoactive intestinal peptide (VIP).[23]

FIGURE 82.1 Neuroblastoma metastatic to liver. Stage 4S neuroblastoma underwent spontaneous regression. (From Snyder HM, et al. Paediatric oncology. In Walsh PC et al. eds., *Campbell's Urology*, 5th edn. Philadelphia: WB Saunders, 1986, 2269. With permission.)

However, this symptom, mimicking malabsorption syndrome, is more often associated with the better-differentiated ganglioneuroma or intermediately differentiated ganglioneuroblastoma. Resolution follows removal of the tumor. Another unusual symptom is cerebellar ataxia and opsomyoclonus (dancing feet, dancing eyes; myoclonic encephalopathy of infants). This syndrome is of unknown pathogenesis and is more often associated with thoracic tumors.[7] While symptoms of catecholamine excess (palpitations, tachycardia, and hypertension) are rare in neuroblastoma, they can occur from excess circulating tumor-derived norepinephrine. However, norepinephrine is less potent than its metabolite, epinephrine, in inducing these symptoms. These symptoms are more commonly found in patients with pheochromocytoma. The responsible enzyme is phenylethanolamine *N*-methyl transferase (PNMT), which plays a role in the conversion of norepinephrine to epinephrine.

Gross, Histologic, Molecular Pathology, and Markers

Neuroblastomas arise from cells of neural crest origin, which ultimately form the sympathetic nervous systems (sympathogonia). The sites of origin may be found at any location in the sympathetic nervous system, with more than one-half occurring in the neonatal abdominal cavity, and up to two-thirds from the adrenal gland. The remainder occur in the sympathetic ganglia and, more rarely, in the organ of Zuckerhandel. The spectrum of biologic behavior or potential of these tumors is broad. Malignant neuroblastomas comprise the majority. Ganglioneuroblastoma and ganglioneuroma represent progressively more benign forms of the tumor, reflecting more indolent clinical manifestations, better prognoses, and distinct morphology and biochemical profiles.

The histopathologic features that define the malignant potential are unique. Homer–Wright pseudorosettes, the diagnostic histologic presence of eosinophilic neutrophils surrounded by neuroblasts, occur in only one-half of cases.[24] The presence of associated neuropils (pigmented neuritic processes) is pathognomonic for neuroblastoma. The other type of cell is the Schwann cell, which may be recruited into the tumor and comprises the Schwannian stroma, which makes up the mesenchymal component of the tumor. The degree of histologic differentiation is classified according to a variety of schemes, but the most popular is that developed by Shimada, which has recently been revised by Joshi (Table 82.2), and a combination of the two is the basis of planned prospective trials.[26,27]

TABLE 82.2 Histopathologic classifications of Shimada and Joshi

Prognosis	Histopathologic Features/Age
Favorable	
Shimada	Stroma rich, all ages, no nodular pattern
	Stroma poor, age 1.5–5 years, differentiated, MKI < 100
	Stroma poor, age <1.5 years, MKI < 200
Joshi	Grade 1, all ages; grade 2, <1 year
Unfavorable	
Shimada	Stroma rich, all ages, nodular pattern
	Stroma poor, age >5 years
	Stroma poor, age 1.5–5 years, undifferentiated
	Stroma poor, age 1.5–5 years, differentiated, MKI > 100
	Stroma poor, age <1.5 years, MKI > 200
Joshi	Grade 2, age >1 year; grade 3, all ages

Source: Brodeur GM, Castleberry RP. Neuroblastoma. In Pizzo PA, Poplack DG, eds., *Principles and Practice of Pediatric Oncology*. Philadelphia: JB Lippincott, 1997, 7712. With permission.

Note: Grade 1 = low mitotic rate (<10 mitotic figures per 10 high power fields) and calcification present; grade 2 = either low mitotic rate or calcification present; grade 3 = neither low mitotic rate nor calcification present.

Abbreviation: MKI, mitosis–karyorrhexis index (number of mitoses and karyorrhexis per 5000 cells).

Molecular Pathology

Molecular understanding of neuroblastoma has identified several newer features of the disease that may aid in all aspects of its management, including diagnosis, natural history, prognostic stratification, and treatment selection. These include analyses of nuclear and chromosomal material, and neuronal phenotyping through assessment of various neuron-associated growth factors. While karyotyping has identified specific chromosomal abnormalities (see below), analysis of DNA ploidy has also revealed significant information. Paradoxically, neuroblastomas of the hyperdiploid variety are more likely to respond favorably to chemotherapy. Diploid or near-diploid tumors are associated with higher-stage disease (including unresectable tumors), poorer prognosis, a lower response to chemotherapy, and recurrence or progression.[28–31]

The most widely reported genetic marker for neuroblastoma has been amplification of the MYCN (or N-myc) proto-oncogene.[22,32] The association between MYCN amplification and high-grade,[33] advanced-stage disease at presentation, rapid progression, and overall poor prognosis is well established. Recently, an etiologic relationship between MYCN and neuroblastoma has been demonstrated by two complementary studies. Chan and coworkers from The Hospital for Sick Children in Toronto reported that elevations in MYCN protein expression in neuroblastoma tissues are independently associated with poor prognosis in high-stage disease (3, 4, and 4S) even in the absence of MYCN gene amplification.[34] Furthermore, MYCN protein levels were prognostic, independent of the most significant variables of age or stage,[34] thus strongly supporting the concept that MYCN expression is directly involved in the cellular events of neuroblastoma progression. Conversely, in the subgroup of patients who did well with normal MYCN gene expression, MYCN protein levels were undetectable.[34] In a related animal study, the targeted overexpression of the MYCN gene in neuroectodermal cells led to the development of neuroblastoma in MYCN transgenic mice.[35] MYCN tumorigenesis is further augmented in the absence of the recognized tumor

suppressor genes NF1 or RB1.[35] This demonstrates that MYCN's transforming effect can be influenced by other genes, consistent with the emerging concept of multistep processes in malignant transformation. MYCN gene amplification is present in approximately 40% of patients with advanced stage 3 or 4 disease (compared with <10% in low-stage patients), and its absence augurs a slower disease progression in these patients.

As mentioned above, deletions of chromosome 1 and gains in chromosome 17 have been shown to carry strong prognostic information in advanced neuroblastoma. A landmark report from a collaborative group in Europe has shown a very powerful association between gains in chromosome 17q and adverse neuroblastoma outcome. The study is important because of its large numbers, the availability of all clinical and genetic data variables for 85% of the patients in the cohort, and the close coordination between a team of basic and clinical researchers. In total, 313 children from six European centers were studied. Often, but not exclusively, the gain of 17q was linked to the loss of 1p. Most significantly, in univariate and multivariate analyses, 17q gain was independently predictive of poor outcome (30.6% 5-year survival with 17q gain vs. 86% 5-year survival without 17q gain).[36]

A longstanding notion in tumorigenesis states that transformation (neoplasia) is the result of aberrant differentiation pathways leading away from the normal cell phenotype. As a result, neuroblastoma may represent an aberration of normal neuronal development. As such, several neuronal differentiation markers have been investigated in this disease, including chromogranin A, neuropeptide Y, and receptors for neurotropins, such as nerve growth factor. Neuropeptide Y is detectable in abundance in the serum of neuroblastoma patients and may be useful in following tumor burden both before and after therapy.[37] In tumor tissue, it reaches its highest levels in poorly differentiated neuroblastoma, compared with ganglioneuroblastoma or ganglioneuroma.[37] Conversely, chomogranin A derivatives may become useful markers of more favorably differentiated tumors.[38]

Acting through various receptors, neurotropic factors are, by definition, involved in the differentiation of neural tissues. One family of neurotropin receptors, the tyrosine kinase receptors TRK-A, TRK-B, and TRK-C, is showing promise in understanding neuroblastoma biology. It appears that TRK-A gene expression is associated with favorable outcome, yielding its highest expression in more well-differentiated tumors.[39,40] Furthermore, TRK-A levels are inversely correlated with MYCN gene expression.[39] Expression of TRK-C and shortened forms of TRK-B also portends a better outcome.[39] Together, these observations have also led to speculation that functioning, intact neurotropin/TRK receptor pathways in these tumors may be further linked to their propensity to mature (differentiate) into ganglioneuromas, or regress through a cell death pathway (from a presumed eventual unavailability of factor for the receptor, or receptor malfunction). However, as our knowledge of the role of these pathways evolves, it is becoming clear that they carry potential as powerful markers of disease, or even as molecular therapeutic targets to manipulate neuroblastomas to assume differentiation or regression pathways.

Drawing on the foregoing discussion, neuroblastomas may be stratified into specific prognostic subgroups based on the genetic interplay represented by MYCN expression, LOH, DNA ploidy, and neurotropin receptor expression. Combined with age and stage, three genetic neuroblastoma profiles can be determined with differing survival rates (Table 82.3).

Diagnosis, Staging, and Treatment

The diagnosis of neuroblastoma is confirmed by histologic sampling of tumor tissue or bone marrow. Standard light and electron microscopic evaluation may be followed by immunohistochemical identification of tissue of neuronal origin. The vast majority of the tumors secrete catecholamines synthesized from the amino acid tyrosine in the following sequence: dopa, dopamine (both excreted as homovanillic acid [HVA]), and finally norepinephrine. In contrast to pheochromocytomas, neuroblastomas lack the ability to convert norepinephrine to epinephrine. Norepinephrine and epinephrine are both excreted as VMA.

Imaging Techniques

Traditionally, the presentation of an abdominal neuroblastoma has been either by the discovery of an abdominal mass on physical examination, or the result of investigations to explain symptoms related to either metastatic disease or the neuroendocrine manifestations of the tumor.

TABLE 82.3 Genetic neuroblastoma profiles

Feature	Type 1	Type 2	Type 3
MYCN amplification	None	None	Present
DNA ploidy	Hyperdiploid	Near diploid	Near tetraploid
LOH	Rare	25%–50%	Present
Neurotropin gene expression	High	Low/absent (except TRK-B, high)	
Age	1 year	>1 year	
Stage	1, 2, 4S	3, 4	
3-year survival	95%	25%–50%	<5%

Source: Adapted from Brodeur G. Clinical and biological aspects of neuroblastoma. In Vogelstein B, Kinzler KW, eds., *The Genetic Basis of Human Cancer*. New York: McGraw-Hill, 1998.

Abbreviation: TRK, tyrosine kinase receptor.

Abdominal ultrasonography will detect a great percentage of those tumors that occur in the abdominal cavity. Occasionally, they are found as an incidental finding in the course of pursuing an otherwise unrelated symptom. With increased sonographic screening, this has now become a more common cause for presentation of these tumors.[42] In the authors' recent experience at a large children's hospital, there have been two instances in the past year when children who were being followed in the course of an investigation for antenatal hydronephrosis had neuroblastomas that became apparent and had not been present on prior examinations (Figure 82.2a–c).

Diagnostic imaging techniques are evolving and improving with great rapidity, and there is no consensus as to which method is best. The choices include ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI). The availability and the noninvasive nature of ultrasonography endorse this technology as the choice for the initial screening test. The time required for both CT and MRI makes their selection for young children more critical. Either of these techniques may be used to delineate and define the extent of the disease. Availability may be the most critical determinant of which should be used. CT imaging currently seems to be the most widely available modality[43] (Figures 82.2 and 82.3).

In seeking metastatic disease, a chest radiograph is a useful initial step. Radioisotope bone scanning using technetium-99m–methylene diphosphonate is more accurate than a standard x-ray skeletal survey for the detection of bony metastases (Figure 82.4).

Prognostic Markers

Both clinical and biochemical markers have evolved that are helpful in the management of neuroblastoma. The best recognized are the traditional clinical parameters of age at diagnosis and tumor stage. Patients diagnosed at 1 year of age appear to show consistently better survival outcomes than older children, even in the presence of advanced disease at presentation. Survival also stratifies dramatically with respect to disease stage, with 75%–90% 5-year survival for stage 1, 2, and 4S patients, compared with 10%–30% 2-year survival for stage 3 and 4 disease.

Various biochemical and cell-associated parameters have also been assessed for their prognostic ability in the management of neuroblastoma. Serum ferritin is elevated

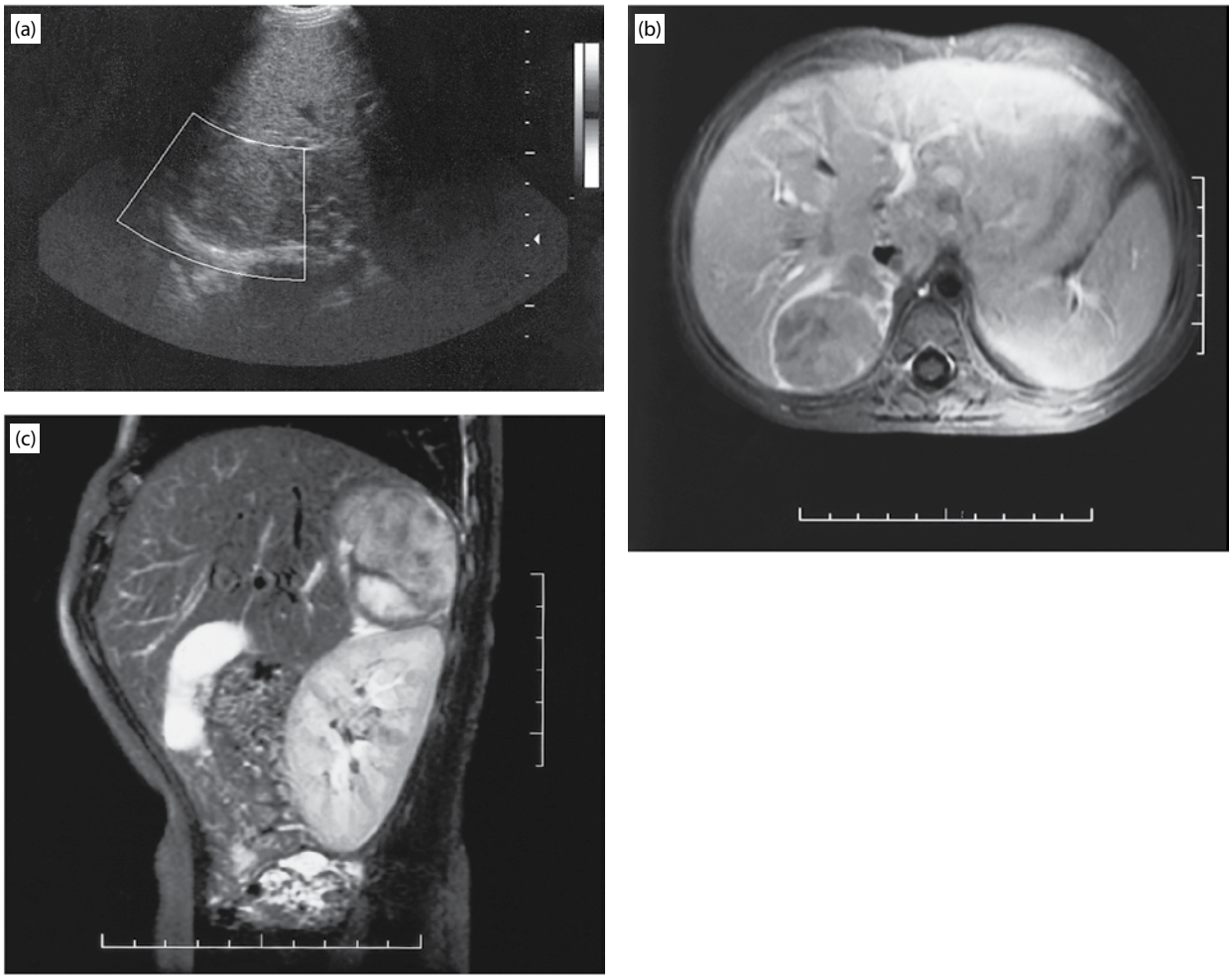

FIGURE 82.2 (a) Ultrasound image discovered in a 1-year-old child as "incidentaloma" in the course of investigating contralateral antenataly diagnosed hydronephrosis. Prior sonogram 6 months earlier with good views of the same area showed no evidence of mass lesion. (b and c) Transverse and sagittal MR images of the same lesion, showing relationships in the retroperitoneum.

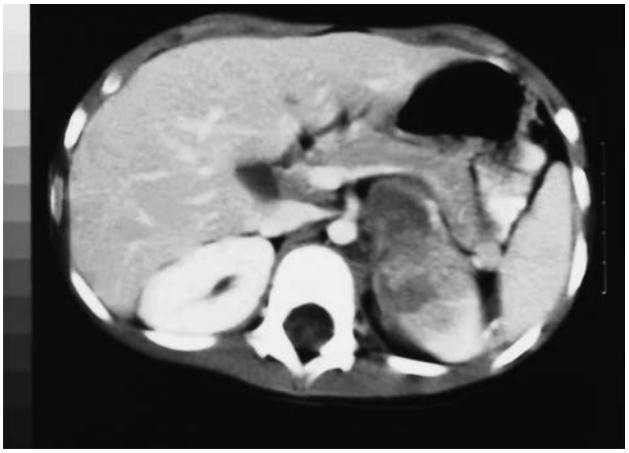

FIGURE 82.3 Transverse CT scan of retroperitoneal recurrence of a previously excised stage 3 neuroblastoma.

during periods of rapid tumor growth and/or large tumor burden. Whether this reflects a growth requirement for ferritin by the tumor or is a product of neuroblastoma cell metabolism is unknown. Ferritin levels appear to discriminate between stage 4 and stage 4S disease.[44] Lactate dehydrogenase (LDH) is elaborated nonspecifically in several tumor types, including neuroblastoma, where it may reflect rapid tumor cell turnover and[44] tumor burden. Neuron-specific enolase is a cytoplasmic enzyme found in cells of neural[45] origin. Neuroblastoma prognosis appears worse if elevated levels are detected in serum, although this marker is not specific to neuroblastoma.[45] Serum and tissue ganglioside GD2 is a glycosphingolipid shed by neuroblastoma tumor cells. It may reflect tumor burden, and decreasing levels may be seen as a positive response to successful reduction of tumor load. The presence of GD2 on the cell surface has attracted interest in targeting this molecule using immunotherapy strategies.[46–48] Finally, matrix metalloproteinases (MMPs) are cellular enzymes required to break down the extracellular matrix and facilitate cell movement through the matrix during the metastatic process. Very recently, tumor cell expression of a membrane-associated MMP was found to correlate with advanced stage and poor outcome in neuroblastoma.[49]

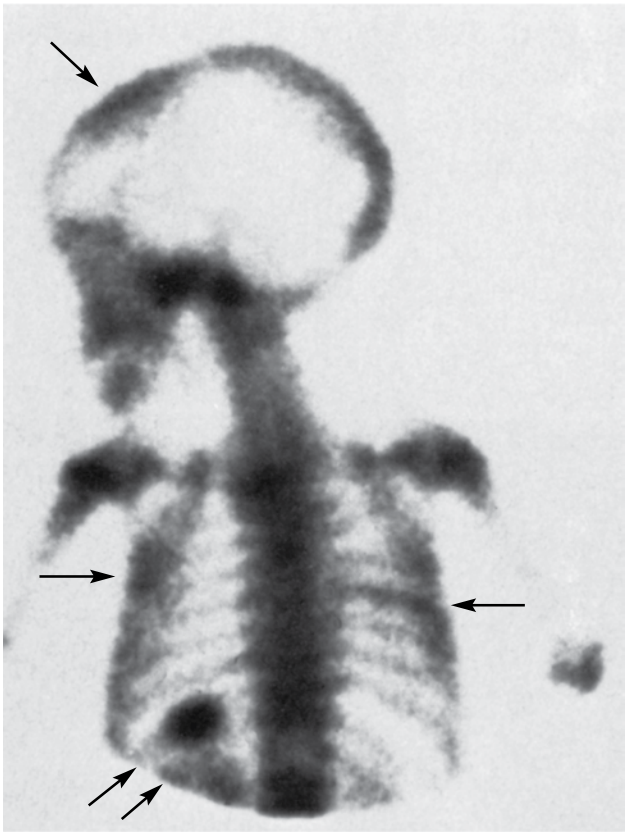

FIGURE 82.4 Posterior view of thorax and skull. Increased uptake is seen in the skull–upper thoracic spine and left and right ribs (arrows) as a result of metastatic neuroblastoma. The decreased uptake at T12 is an unusual manifestation of metastatic tumor. The right suprarenal uptake of tracer is within the primary tumor (double arrow).

Staging

A disease with such diverse manifestations as neuroblastoma in childhood needs a comprehensive staging system to allow precise diagnostic criteria and a method for categorizing and quantifying disease. Such a staging system then acts as a template upon which diagnostic criteria can be applied to various subgroups of disease, and permits definition of outcome measures that will allow collaboration between centers in implementing and assessing clinical trials. An international working group published the outcome of its deliberations in 1988.[50] The staging system recommended is known as the International Neuroblastoma Staging System (INSS), and the response criteria are referred to as the International Neuroblastoma Response Criteria (INRC). This staging system has now replaced previous systems by Evans, originally established by the Pediatric Oncology Group (POG). Table 82.4 outlines the three staging systems, thus facilitating some comparison of previously published data.[51–53]

Treatment

Therapy of neuroblastoma requires close coordination of medical, surgical, and radiation oncologists and clearly represents a prime example of multimodal cancer therapy. Surgical intervention plays a dual role. At the time of diagnosis, open or laparoscopic approaches may be necessary to obtain adequate and thorough samples for histologic and molecular diagnosis and marker analysis. Needle biopsy materials are most often inadequate for these purposes. For selected tumors, primary surgical excision may be possible, particularly for small, locally confined cases. In this regard, laparoscopic surgery may be considered and has been used successfully for small tumors identified by screening.[54] Given that infant screening detects tumors that are generally biologically favorable, laparoscopic surgery may be a safe modality on oncologic grounds. Open surgical dissection is also employed to both assess response to therapy and excise residual disease after initial courses of chemotherapy have been completed. Recent reports have suggested a higher incidence of nephrectomy in children with neuroblastoma who were treated with primary surgical intervention.[55,56]

TABLE 82.4 Neuroblastoma staging system

Evans and D'Angio	POG	INSS
Stage I	*Stage A*	*Stage 1*
Tumor confined to the organ or structure of origin.	Complete gross resection of primary tumor, with or without microscopic residual. Intracavitary lymph nodes, not adhered to and removed with primary (nodes adhered to or with tumor resection may be positive for tumor without upstaging patient to stage C), histologically free of tumor. If primary in the abdomen or pelvis, liver histologically free of tumor.	Localized tumor with complete gross excision without microscopic residual disease; representative ipsilateral lymph nodes negative for tumor microscopically (nodes attached to and removed with the primary tumor may be positive).
Stage II	*Stage B*	*Stage 2A*
Tumor extending in continuity beyond the organ or structure of origin but not crossing the midline. Regional lymph nodes on the ipsilateral side may be involved.	Grossly unresected primary tumor. Nodes and liver same as stage A.	Localized tumor with incomplete gross excision; representative ipsilateral nonadherent lymph nodes negative for tumor microscopically.
Stage III	*Stage C*	*Stage 2B*
Tumor extending in continuity beyond the midline. Regional lymph nodes may be involved bilaterally.	Complete or incomplete resection of primary. Intracavitary nodes not adhered to primary histologically positive for tumor. Liver as in stage A.	Localized tumor with or without complete gross excision, with ipsilateral nonadherent lymph nodes positive for tumor. Enlarged contralateral lymph nodes must be negative microscopically.
Stage IV	*Stage D*	*Stage 3*
Remote disease involving the skeleton, bone marrow, soft tissue, distant lymph node groups, etc. (see stage IV-S).	Any dissemination of disease beyond intracavitary nodes (i.e., extracavitary nodes, liver, skin, bone marrow, and bone).	Unresectable unilateral tumor infiltrating across the midline, with or without regional lymph node involvement; or localized unilateral tumor with contralateral regional lymph node involvement; or midline tumor with bilateral extension by infiltration (unresectable) or by lymph node involvement.
Stage IV-S	*Stage DS*	*Stage 4*
Patients who would otherwise be stage I or II, but who have remote disease confined to the liver, skin, or bone marrow (without radiographic evidence of bone metastases on complete skeletal survey).	Infants of $<$1 year of age with stage IV-S disease (see Evans and D'Angio).	Any primary tumor with dissemination to the distant lymph nodes, bone, bone marrow, liver, skin, and/or other organs (except as defined for stage 4S).
		Stage 4S
		Localized primary tumor as defined for stage 1, 2A, or 2B with dissemination limited to the skin, liver, and/or bone marrow (limited to infants of $<$1 year of age).

Source: From Halperin EC et al. Neuroblastoma. In Halperin EC, ed., *Pediatric Radiation Oncology*, 2nd edn. New York: Raven Press, 1994, 182–3.

Chemotherapy is a major component of the treatment of neuroblastoma. Both single-agent and synergistic multiagent drug regimens are used, combining cell cycle–specific and cell cycle–independent drugs to achieve the maximum ratio of therapeutic benefit to toxicity. Ionizing radiation has a role in neuroblastoma treatment as the tumor is radiosensitive. It is most useful in achieving local control, on the one hand, and palliation of disease uncontrollable by other modalities, on the other. As a primary modality, however, radiotherapy is limited by the extensive metastatic proclivity of many neuroblastomas. The agent methyliodobenzylguanidine (MIBG), used in the localization of neuroblastomas and pheochromocytomas, has been studied for its ability to bind to neuroblastoma tumors systemically and carry with it radioligands such as iodine-131 that are toxic to the tumor cells.[48,57,58] This approach has also been used as a surgical adjunct to guide tumor tissue resection using the gamma camera intraoperatively once the tumor is radiolabeled by preoperative injection of [^{131}I]MIBG.[59]

Given the aggressive nature of advanced- and higher-staged disease, efforts continue to attempt improved disease control in this subset of patients while refining therapy to limit toxicity in lower-stage and more favorable disease.

Treatment Strategy

The ability to stratify patients into distinctly risk-related groups, by application of the varied but highly accurate histologic and molecular diagnostic and staging methodologies, has permitted the much more judicious and specific use of the therapeutic regimens.

Stage 1 and 2 tumors (low risk) are treatable by primary surgical resection alone, with no need for initial chemotherapy or radiotherapy. A prognosis of up to 89% survival has been reported in this group of patients.[2,58,60] Stage 4S tumors will undergo spontaneous remission and are thus considered low risk. However, if symptoms are present related to severe hepatic metastatic disease or respiratory compromise, they may benefit from chemotherapy or radiation therapy in small doses.

Stage 3 tumors (intermediate risk) still have an excellent overall survival rate of up to 89%,[60] but chemotherapy is advised following primary surgical excision. Second-look surgery may also be appropriate after chemotherapy. The goal of therapy in this group is to reserve more intense therapy for those children with biologically unfavorable tumors.

Patients with stage 4 disease (high risk) have derived minimal benefits from even the most intensive regimens. Multiagent chemotherapy remains the standard primary treatment strategy for these patients. There have been isolated applications of ablative chemotherapy and bone marrow transplantation, and these intensive therapeutic approaches are currently being explored in multicenter trials. The overall prognosis in this group of children remains very low (15%–35% survival).[61]

Ganglioneuroma

A more histologically benign counterpart of neuroblastoma is the ganglioneuroma. Ganglioneuroblastoma is an intermediate malignant classification between ganglioneuroma and neuroblastoma, and for treatment purposes is regarded with neuroblastoma. Ganglioneuromas are most often seen in older children and present as abdominal masses. It is intriguing to hypothesize that late development of a more benign variant may represent a "second hit," but these tumors do not exhibit an "explosive" form of metastatic behavior.[62] Nonetheless, by virtue of their inexorable growth and distortion of adjacent tissues, they can have a very morbid clinical course. Such a case is illustrated in Figure 82.5a–c, in which both gastrointestinal and genitourinary tissues are grossly displaced. The urologic system, in particular, may exhibit such profound destruction that urinary diversion may be deemed necessary. The figures illustrate the results of MRI, which can provide eloquent detail of the soft tissue involvement by these tumors, while there is no evidence of direct histologic invasion of the compressed tissues (Figure 82.6).

The correlation of the MRI features with latent malignant potential in these tumors has recently been documented by Ichikawa et al.[63] They were able to show that punctate calcification on the CT scan and low or intermediate attenuation are common in ganglioneuromas. The MR images are mainly of low intensity on T_1-weighted images and of high intensity on T_2-weighted

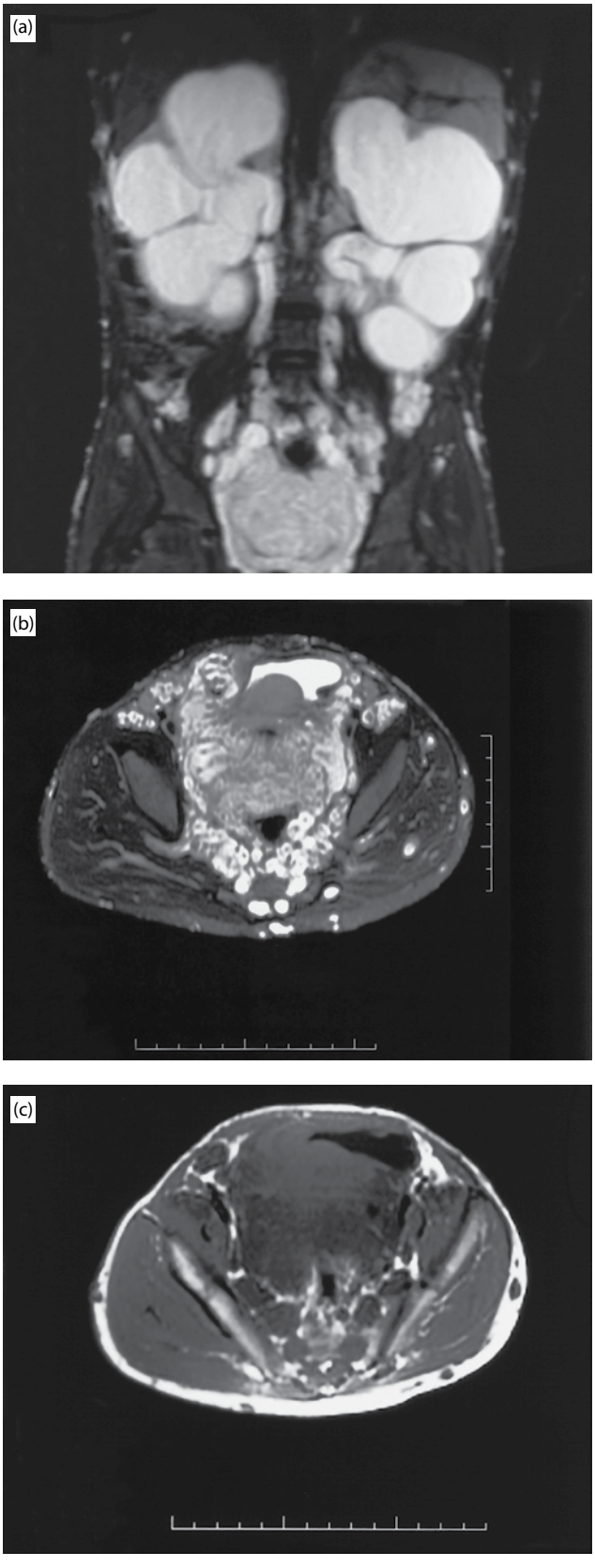

FIGURE 82.5 (a) MR scan of a patient with a ganglioneuroma, showing obstruction of the ureters. (b) Primary neuronal masses displacing the bladder anteriorly and the rectum posteriorly. (c) T_2-weighted image of the same pelvic area as in (b), showing the different appearance of neural tissues.

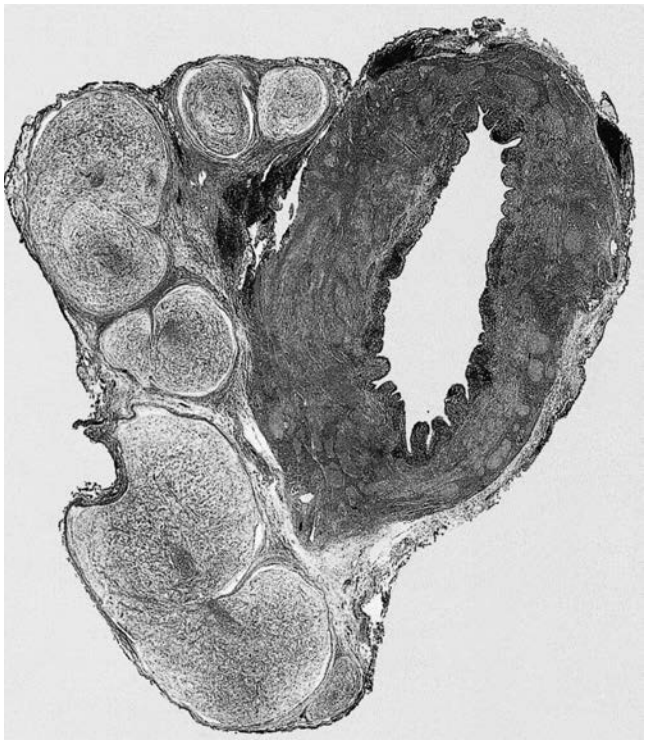

FIGURE 82.6 Pathologic section of area of excised ureter, with ureter encased in, but not invaded by, tumor tissue.

images. Dynamic MR studies show a lack of early involvement but gradually increasing enhancement. The authors concluded that the absence of these features, judged "typical" for ganglioneuroma, should suggest a potential for a more malignant course. The slow-growing nature of ganglioneuromas may also have a devastating effect on vascular and neurologic function by virtue of its compressive effects on adjacent structures. Figure 82.7 demonstrates extension along the sacral nerve prior to the appearance of clinical degeneration. This and other cases have demonstrated the potential for clinical morbidity that may be associated with ganglioneuroma despite its nonmetastatic nature. To prevent these localized effects, incomplete surgical resection may be justified in the absence of effective chemotherapy or radiotherapy.

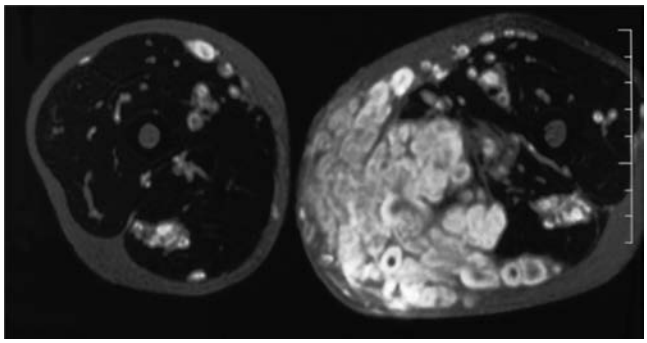

FIGURE 82.7 Extension of ganglioneuroma down the sheath of the sacral nerve.

PHEOCHROMOCYTOMA

Clinical Features and Presentation

Pediatric pheochromocytoma is an extremely uncommon primary tumor of the adrenal medulla, although it is the most common hyperfunctioning form of this tissue in children. Over a period of 5 years at The Hospital for Sick Children in Toronto, of 30 patients presenting with a primary adrenal tumor, only 1, a 16-year-old girl, had a pheochromocytoma. The tumors arise in the autonomic system, with 90% originating in the adrenal gland. Catecholamine production is the norm and is the basis for both the clinical manifestations and laboratory diagnosis. Pediatric pheochromocytomas can be seen in association with a variety of diseases, including neurofibromatosis, von Hippel–Lindau disease, Sturge–Webber syndrome, and multiple endocrine neoplasia (MEN-2). Those associated with MEN-2 are more likely to occur later in life and are more likely to be bilateral.

Imaging, Biochemical Features, and New Prognostic Markers

The diagnosis of pheochromocytoma in childhood is suggested by the rare coexistence of hypertension and abdominal mass detectable on sonographic evaluation. Nonpalpable pheochromocytoma causing secondary hypertension in children is exceedingly rare. The diagnosis is confirmed by means of either serum or urine confirmation of hypersecretion of catecholamines.

As stated previously, the principal catecholamine that produces the classic characteristic symptoms of flushing, palpitations, hypertension (vasoconstriction), and anxiety in patients with pheochromocytoma is epinephrine. Epinephrine is a metabolite of its precursor, norepinephrine. The latter is a less potent mediator of the clinical constellation seen in pheochromocytoma. However, compared with neuroblastoma, both catecholamines are more commonly produced by pheochromocytomas. Pheochromocytomas, particularly those of adrenal origin, produce the enzyme PNMT, which converts norepinephrine to epinephrine. As such, the norepinephrine-to-epinephrine ratio has been used to distinguish pheochromocytomas of adrenal from those of extraadrenal origin.

With respect to diagnostic imaging, the initial methodology in suspected cases is ultrasonography (Figure 82.8). Thereafter, either CT or MRI can be employed to confirm the diagnosis of an adrenal or a para-adrenal mass (Figure 82.9). Serologic or creatinine-specific measures of catecholamine excretion in the urine are then undertaken. The most specific diagnostic imaging methodology is radionucleotide scanning using [^{131}I]MIBG scintigraphy (Figure 82.10). With this approach, the sensitivity is greater than 90%.[64] [^{131}I]MIBG scanning is particularly valuable in the localization of tumors located outside the adrenal gland.[65,66]

One of the persisting challenges in pheochromocytoma management remains the inability to define precisely whether a given tumor is benign or malignant. The current gold standard criterion for malignancy remains the

FIGURE 82.8 Ultrasound image of a left suprarenal tumor in a 16-year-old child presenting with hypertension.

appearance of metastases. As a predictor of malignancy, this is analogous to predicting that automobile brakes are defective based on the occurrence of a collision. Clearly, more accurate markers for determining the malignancy of pheochromocytoma are needed. Recent studies have identified biologic features of pheochromocytomas that may hold promise in determining the metastatic proclivity of the tumor. For example, telomeres are composed of repeated nucleotide sequences on the ends of chromosomes. During normal cell aging, they progressively shorten during successive normal cell replications. In normal cells, this shortening is thought to be associated with waning activity

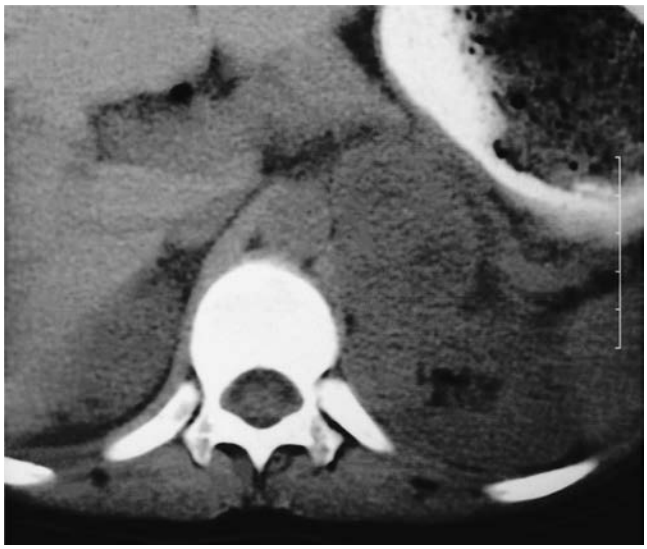

FIGURE 82.9 CT image of left suprarenal pheochromocytoma, as seen in ultrasound in Figure 82.8.

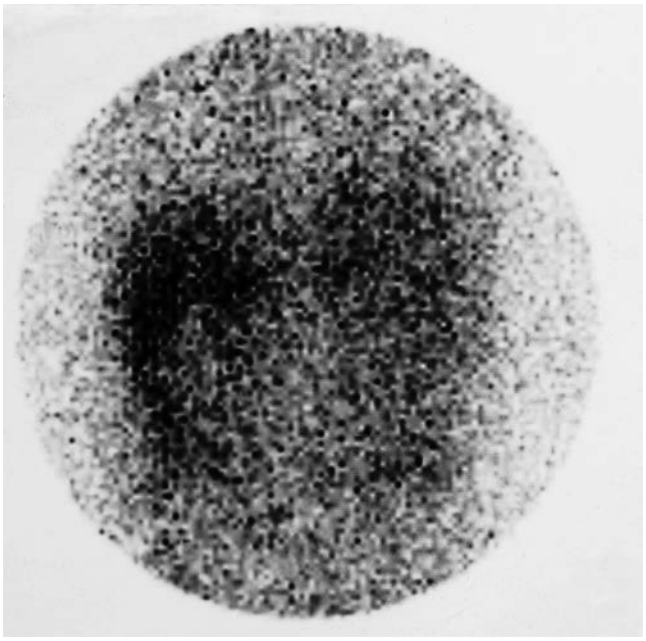

FIGURE 82.10 MIBG abdominal scan, with uptake of radionuclide in the left suprarenal area, in a 16-year-old with pheochromocytoma.

of the enzyme that produces the telomeres. Recent retrospective molecular analysis of pheochromocytoma tumors known to be benign or malignant reveals that telomerase, the RNA polymerase enzyme responsible for the production of telomeres, shows increased activity exclusively in tumors known to be malignant.[67,68] Similarly, antibody-based approaches that detect proliferating cells are being used increasingly to describe the malignant phenotype in tumors. One such antibody, MIP-1, selectively recognizes cells engaged in the cell cycle (i.e., scheduled to undergo mitosis, but not necessarily in the process of mitosis). Its predictability was explored in a survey of pheochromocytomas in which malignancy was confirmed by the existence of metastases. A positive MIB-1 labeling index (defined as >3% of tumor cells staining positive for MIB-1 vs. the total number of cells counted) showed a specificity of 100% (benign tumors stained negative) and sensitivity of 50% (half of the malignant tumors stained positive).[69] Although sensitivity was poor, the ability to define benign disease accurately in this manner would be clinically reassuring.

Therapy

The historic importance of pheochromocytomas with respect to surgery is not the technical nature of their excision, but the associated anesthetic risks. These relate to the potential for drastic changes in the excretion of catecholamines upon manipulation and subsequent removal of the tumor. The challenges revolve around stabilization of blood pressure intraoperatively and the prevention of potential cardiovascular collapse at the time of tumor removal or ligation of the veins delivering catecholamines to the systemic circulation. In infants, particularly in the preoperative state, these risks pose a great concern. In view

of the high specificity and reduced invasiveness of modern serologic and radionuclide diagnostic methodologies, risk factors are reduced. As in adults, the mainstay of preoperative therapy includes blockade of α-adrenergic receptors (phenoxybenzamine) accompanied by adequate systemic volume repletion once the vasoconstrictive and volume-contracted state has been overcome. Cardiac β-blockade (propranolol) in every case to prevent reflex tachyarrythmias remains controversial but should at least be considered in selected cases. Clearly, preoperative pharmacologic management of affected children should be undertaken in collaboration with the pediatric endocrinologist and anesthesiologist. If adequate blockade and volume replacement are achieved preoperatively, manipulation of the tumor is usually not accompanied by large variations in blood pressure, and large additional volume requirements are usually not found necessary upon tumor removal.

Open surgical excision by the flank or posterior lumbotomy approach has been the classic means of treatment. However, Rutherford et al.[70] have published an excellent review of the laparoscopic experience of excision of these tumors. They noted that patients treated laparoscopically have a significant reduction in recovery time, as well as a low complication rate. It may well be that this will become the most widely accepted method of surgical excision.

SACROCOCCYGEAL TERATOMA

SCT is the most common neoplasm in the newborn, and one of the first tumors successfully excised surgically.[71] Virchow coined the term *teratoma*, referring to a coccygeal growth with diverse anatomic characteristics. The tumors originate from all three embryologic tissues: ectoderm, mesoderm, and endoderm. Although they have provoked great interest because of their occurrence early in life and their dramatic appearance at birth, they have achieved even more current interest because of the facility and frequency with which they can be diagnosed by antenatal ultrasonography.[72–77] The appearance and character of the tumors are highly variable since they may be internal or external. SCTs have no known etiology. They are usually benign, but may undergo malignant degeneration.

Pathology

A teratoma is a neoplasm composed of multiple tissues that are foreign to the area in which it arises. Teratomas are grouped into those benign lesions with mature tissue (70%), those having malignant anaplastic elements (20%), and a third, embryonic group (10%), which may contain histologically immature-appearing benign tissue that does not progress to mature organ formation.[78] This latter group carries a generally favorable prognosis following total excision. In the benign varieties, elements such as skin, teeth, central nervous system (CNS) tissue, cartilage, bone, and respiratory and alimentary mucosa may be seen.

Infants diagnosed with SCT at greater than 1 year of age, as well as older children, are more likely to have malignant elements. To detect these elements, the pathologist must undertake an extensive search through all the varied elements within the tumor. The term *yolk sac* or endodermal sinus tumor is the name appropriately used for the malignant elements in such tumors. These tissues represent a separate element of the teratomatous cell line. Elevated serum levels of α-fetoprotein may be seen in these cases.

Clinical Features and Presentation

The traditional mode of presentation of these tumors has been discovery at birth. In most developed countries where antenatal sonography is now either mandatory or prevalent, they are discovered by antenatal sonography.[73–77] A recent review[79] of antenatally diagnosed SCTs demonstrated a high incidence of *in utero* mortality (19%) coupled with a perinatal mortality of 14%. The incidence of premature labor in this series was 50%. Thus, although the pathology of SCT is often benign, the overall outcome is associated with considerable morbidity and mortality. Those clinical features in the antenatal state that correlated with a poorer prognosis included polyhydramnios (an early sign of fetal distress and predictor of placental megaly-hydrops fetalis), tumor hypervascularity or the presence of a solid tumor (a risk factor for both malignancy and vascular steal syndrome), large tumor size at delivery (>10 cm in its greatest dimension), and a fast rate of tumor growth relative to cranial growth.

A solid tumor is the most ominous predictor of poor outcome. A fetus with a solid tumor has a mortality rate of 66% compared with a mortality of 11% for cystic or mixed tumors. Thus, mothers carrying a fetal diagnosis of SCT at the time of clinical obstetric presentation are definitely at risk for prenatal and perinatal complications. The presence of polyhydramnios appears to be a relative predictor or warning sign of premature labor.

There is a 5%–25% association with other congenital anomalies in infants with benign SCT. Seventy-five percent of the infants are female, harboring primarily benign tumors. The sex distribution is more evenly distributed between males and females in those whose tumors develop malignant degeneration.

Classification

The classification of SCT was proposed in 1974 by Altman and includes type 1, totally external; type 2, primarily external with an internal component; type 3, almost completely internal; and type 4, totally internal (Figure 82.11).[80]

Today, since most SCTs may well be diagnosed in the antenatal state following obstetric ultrasonography, an improved prognosis may be anticipated following delivery by cesarean section. The latter is advised as an initial attempt to decrease perinatal mortality and morbidity. The major early cause for morbidity relates to tumor rupture, for which cesarean section is the best prophylaxis. In Altman's classification, large tumors were defined as being greater than 10 cm, and these appear to be associated with greater morbidity.

When not diagnosed prior to birth, external tumors are found at delivery. Internal tumors may present as an abdominal mass, with the diagnosis of SCT noted by neonatal ultrasonography.

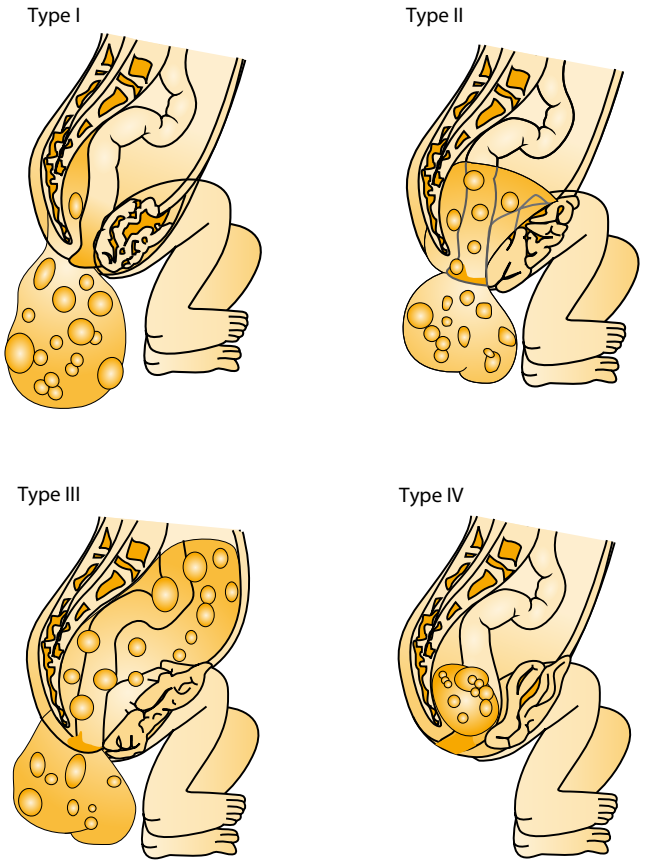

FIGURE 82.11 Classification of SCTs. Type I: Tumors are predominantly external (sacrococcygeal) with only a minimal presacral component. Type II: Tumors present externally but with a significant intrapelvic extension. Type III: Tumors are apparent externally, but the predominant mass is pelvic and extends into the abdomen. Type IV: Tumors are presacral with no external presentation. (From Altman RP et al. *J Pediatr Surg* 1973;9:389. With permission.)

Laboratory

Tumors that undergo malignant degeneration may produce α-fetoprotein and/or β-human chorionic gonadotropin (β-hCG). These proteins are indicators of malignant degeneration in the dermal sinus or choriocarcinomatous components of the tumor.[71,81]

Imaging

Imaging studies for complete assessment include CT and MRI. Radiographic detection of calcification does not distinguish between benign and malignant tumors (Figures 82.12 and 82.13).

Treatment

With the increasing availability of antenatal diagnosis, the question of antenatal intervention has had a logical appeal. Other forms of intrauterine therapy, such as intrauterine transfusion and decompression of a dilated urinary tract, have been successful as early as 16 weeks' gestational age. However, large or completely external SCTs have not yet been uniformly successfully approached surgically.[82,83] It has been speculated that ligating the blood supply to the tumor prenatally may be effective in decreasing its size and/or controlling the hyperdynamic state in the perinatal period.[84,85] In spite of the attractive apparent potential for intrauterine treatment, no success has been seen in antenatal treatment or antenatal surgical excision.

Postnatal therapy of SCT is primarily surgical. Devascularization of the tumor may be of benefit; however, this is best applied as the first intraoperative component of surgical removal.[84,85] Complete surgical excision should be the rule, with *en bloc* removal of the involved portion of the coccyx.

The two clinical groups of presentation include those that appear early in the neonatal period with large, benign tumors, and those that appear later (>1 year of age),

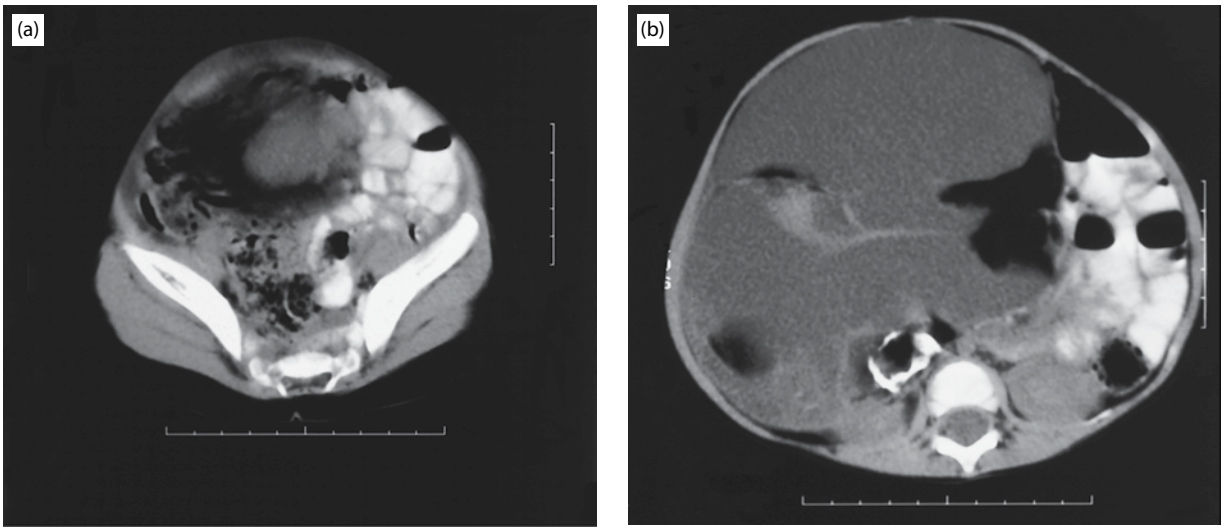

FIGURE 82.12 CT images of cystic teratoma in a 6-month-old child, arising from the pelvis (a) and filling the abdomen (b).

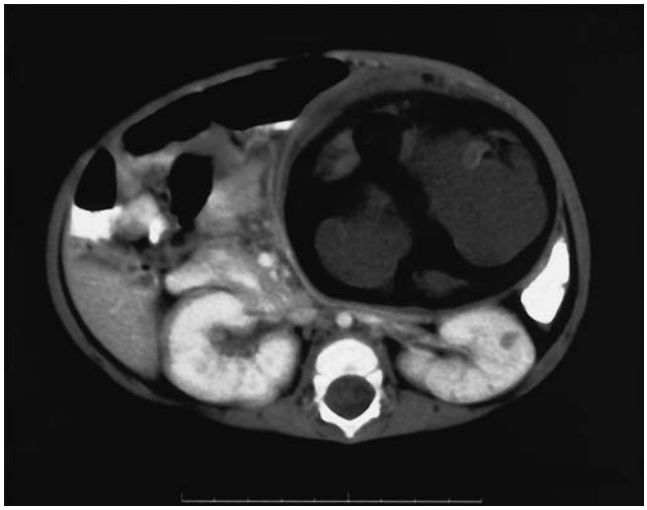

FIGURE 82.13 CT image of a more solid teratoma filling the central abdomen in a 6-month-old child.

which are often smaller, fixed, and malignant. In the first group, total removal is the rule and is best achieved by a midline sacral or chevron incision. The coccyx should be removed in the process of excising the tumor. With the retroperitoneal extension of the teratoma, urinary, internal genital, and gastrointestinal organs may be displaced. They can usually be dissected free, with minimal injury to the viscera, and good access to the vascular supply of the tumor is usually afforded by this retroperitoneal approach. However, in more extensive cases, anterior abdominal exploration may be warranted. A generous surgical exposure to obtain control of the presacral vessels is recommended. Avulsion of the vessels is a hazard to be avoided. In some rare instances, SCT may involve the dura or extend to the spine. This potential extension can be defined by meticulous preoperative imaging.[86–88] An inadvertent entry into the dura may result in a cerebrospinal fluid leak, which is associated with a higher morbidity. Modern imaging techniques, particularly MRI, will allow a much more achievable definition of these potential extensions to the CNS.

The second group of patient presentation is represented by those children in whom tumors present at an age beyond 1 year. These tumors are generally symptomatic, fixed, and firm. Diagnosis is established by ultrasound and/or physical examination and confirmed by CT or MRI. These tumors are often of a malignant variety, and serum α-fetoprotein is a sensitive marker. The appropriate surgical approach is initially directed at biopsy, followed by either multiagent chemotherapy or radiotherapy, in an attempt to decrease the size of the tumor, followed by surgical removal.

Results of Therapy

There are only rare reports of success in therapy in the antenatal stage.[83] In postnatal excisions, those undertaken in infancy for both external and internal SCT are remarkably successful in achieving complete removal of tumors with relatively little long-term morbidity.[89,90,91] Incontinence is rare. However, in those cases where high sacrococcygeal extension is present, necessitating transabdominopelvic excision, long-term fecal soiling and incontinence may be more prevalent. These sequelae may be related to more direct injury of skeletal muscular components or to some more occult neurogenic impairment of the viscera.[92] These sequelae may also be seen in the newborns after the excision of large, benign tumors.

Malignant SCT is rare in children under 6 months of age, but beyond that, the incidence rises sharply.[93] Malignant tumors may invade adjacent tissues or may recur in up to 40% of cases. During the 1990s, chemotherapeutic regimes added considerably to the improved outcomes.[94–97]

Long-Term Follow-Up

A recent evaluation of long-term follow-up in children with SCT showed that mature teratomas may have a recurrence rate of up to 11%. Further treatment with surgical excision and combined chemotherapy resulted in an 85% cure rate.[98] On long-term follow-up, a 3% recurrence rate was noted for immature teratomas. They were detected by a rising α-fetoprotein level 6 months after the initial procedure. These responded well to local excision. Endodermal sinus tumors detected and treated initially with surgical excisions represented only 9% of the tumors presenting at birth, whereas they represented 27% of the patients presenting at an older age. With long-term follow-up, 89% are still alive in spite of the higher recurrence rate.

ADRENAL CARCINOMA

Adrenal carcinoma represents fewer than 0.0001% of neoplastic tumors in children. The most common presentation is abnormal virilization, occurring in two-thirds.[99] Symptoms consistent with Cushing's syndrome account for most of the remainder. Individual case reports have reported occasional aldosterone-secreting tumors. Given the widespread availability of ultrasound imaging technology, the most common presentation may now be that of an incidental finding on an abdominal ultrasound.

Adrenocortical tumors may also be a component of more global genetic malformations. These include children with congenital adrenal hyperplasia, multiple endocrine syndromes (MEN-1), and Beckwith–Wiedemann syndrome.

Clinical Presentation

Virilizing Adrenal Tumors

Of the functioning adrenal cortical tumors, virilizing forms account for two-thirds, usually occurring in children older than 2 years. The tumors produce dehydroepiandrosterone (DHA), a weak androgen but one that is converted to Δ-4-androstenedione and testosterone, which are more potent virilizing hormones. Boys with such tumors present with signs of precocious puberty. Girls respond with an increase in clitoral size, similar to that seen with congenital adrenal hyperplasia (Figure 82.14). Pubic and axillary hair may be seen in children of either gender.

FIGURE 82.14 Virilizing adrenal carcinoma in a 5-year-old girl. Note the clitoral hypertrophy and pubic hair. There is no posterior labial fusion, as would be seen in congenital adrenal hyperplasia.

Alternate causes of premature virilization in boys include interstitial cell tumors of the testis or a delayed manifestation of congenital adrenal hyperplasia. Clinical evaluation may give some clues toward distinguishing the underlying etiology. Unilateral or asymmetric testicular enlargement suggests a Leydig cell tumor. In patients with centrally stimulated precocious puberty, testicular enlargement is bilateral. With virilizing adrenal tumors, the testes are usually small.

The differential diagnosis in female children includes ovarian arrhenoblastoma and other rare tumors of the adrenal cortex.

Cushing's Syndrome

Approximately one-third of children with adrenocortical tumors have the stigmata of Cushing's syndrome. Carcinoma may be responsible in up to one-half, with the others having bilateral adrenal hyperplasia. A benign adenoma may rarely be seen. The clinical appearance is in response to the excessive production of cortisol. This leads to protein catabolism, increased gluconeogenesis, and the typical obesity associated with cortisol excess. The moon facies and truncal obesity (Figure 82.15) of Cushing's disease are generally obvious when they are present in infants.

The differential diagnosis in patients exhibiting excess adrenocortical activity includes adrenal adenomas and iatrogenic administration of steroids. This latter iatrogenic excess is commonly seen in children receiving transplanted organs.

Feminizing Adrenal Tumors

Feminizing adrenal tumors are rare. They occur more frequently in males, and in these cases, the more commonly seen primary gynecomastia must be excluded.

Diagnostic Evaluation

The critical diagnostic feature is the biochemical demonstration of adrenal hyperfunction. Urinary steroids typically show a markedly elevated 17-ketosteroid level. The free cortisol, DHA, and 17-hydroxysteroid levels may also be elevated.[100] Radioimmune assays of serum hormonal levels usually show elevation of DHA, Δ-4-androstenedione, testosterone, and cortisol.[101,102] Serum estrogen levels are elevated in the rare feminizing cases.[103] Occasionally, an elevated serum aldosterone level can be demonstrated in cases of adrenocortical carcinoma.[104]

In Cushing's syndrome caused by adrenocortical carcinoma, the plasma cortisol level and urinary corticosteroids are markedly elevated above the levels typically seen with adrenal hyperplasia or an adrenal adenoma. A significant elevation in 17-ketosteroids, pregnanetriol, and estrogens may suggest carcinoma. The adrenocorticotropic hormone (ACTH) stimulation test produces no change in adrenocortical carcinomas, whereas those with adrenal hyperplasia show an exaggerated normal response. In exogenous obesity, which occasionally may enter the differential diagnosis, the ACTH test result is normal. When benign adenomas are present, the ACTH test exhibits a subnormal response. Metyrapone blocks 11-hydroxylation in the adrenal cortex and leads to a fall in cortisol level with an increase in endogenous ACTH. Thus, a test with metyrapone produces results similar to those produced by the ACTH test. The diurnal variation usually seen in normal cortisol levels is absent with both tumors and adrenal hyperplasia. Dexamethasone blocks ACTH release in normal patients. The dexamethasone suppression test is useful to separate adrenal hyperplasia from tumors in that a large dose (8 mg) typically suppresses hyperplasia but not a tumor (Table 82.5).[105,106]

Modern diagnostic imaging has led to the greatest advances over the past decade. (See the "Imaging Techniques" section under "Neuroblastoma.") In addition to the ultrasound findings, MRI scanning has led to tremendous advances in the ability to distinguish adrenal carcinoma from benign adenomas.[107,108]

Treatment

Treatment of adrenal cortical carcinoma is surgical. In children, open surgical removal may be accomplished by large, transverse abdominal incisions or, in some instances, by extended flank incisions. Laparoscopic removal is now widely used in adults, but the current lack of small instrumentation limits its use in children.[109] The advances in imaging allow more limited surgical approaches than may have been previously encountered. A tumor diameter of more than 5 cm is a reasonable predictor of malignancy, whereas small adenomas may be approached in a more limited manner. Preoperative care must recognize the need for corticosteroid replacement in cases where corticoid excess is anticipated.

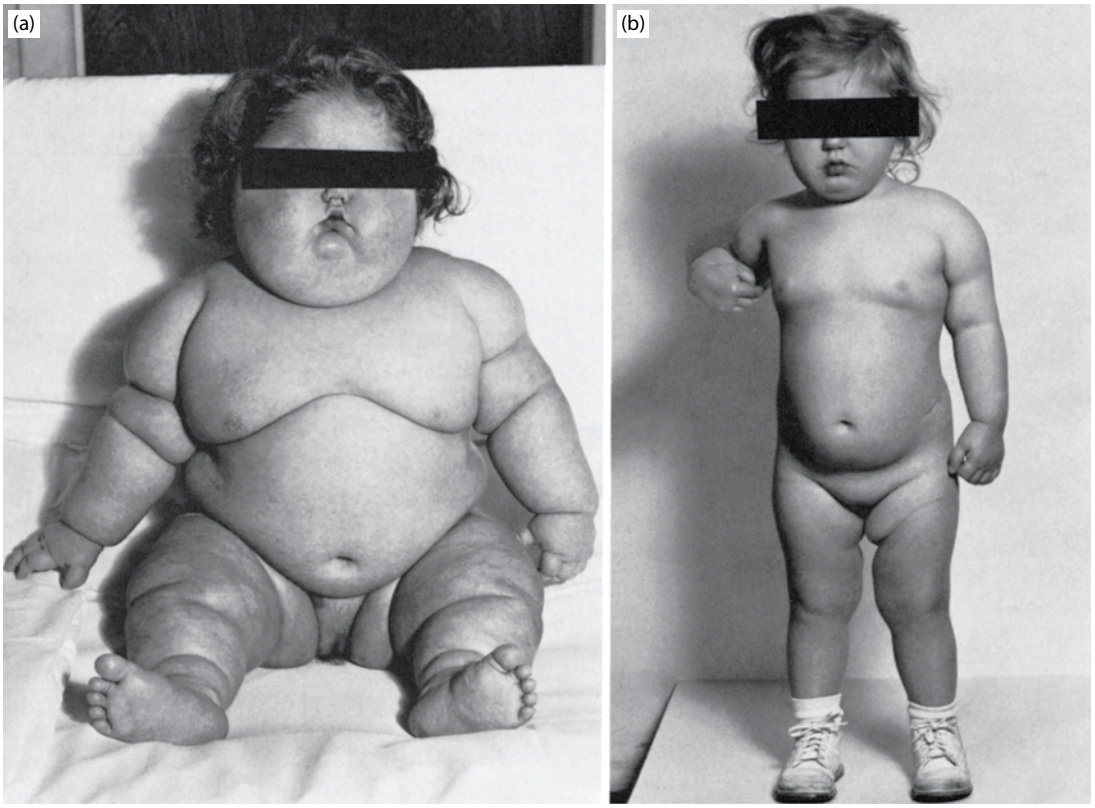

FIGURE 82.15 (a) Striking features of cortisol excess in a 17-month-old girl with adrenocortical carcinoma. In addition, pubic hair and mild enlargement of the clitoris were present. (b) At 10 months after removal of the adrenocortical carcinoma, there was complete regression of the signs of Cushing's syndrome.

The prognosis for adrenal carcinoma is poor. Surgery is the primary motive therapy, and chemotherapy has not been effective in controlling widespread disease.

LYMPHANGIOMAS

Lymphangiomas are benign tumors composed of a mass of anastomosing lymphatic channels. These are rare and most commonly affect the extremities. Most are congenital and may not become evident until a few years of age. When in the retroperitoneum, they are found by the evaluation of abdominal pain, which may be caused by the onset of spontaneous hemorrhage into the mass. However, they may extend through the inguinal canal and present with the misdiagnosis of hernia. Diagnosis is made on CT, at which time the low-density characteristic of lymphatic tissue is noted.

Surgical excision of the majority of the wall of the tumor is ideal, but may not be technically possible without causing significant damage to adjacent organs. Large cysts may be drained into the peritoneal cavity.

NEUROFIBROMA

Patients with neurofibromatosis (von Recklinghausen's disease) may present with abdominal neurofibromas similar to, but as a more benign variant of, ganglioneuromas. As

TABLE 82.5 Test results with various adrenocortical lesions

	Plasma cortisols		Dexamethasone test[a]			
Condition	**Concentration**	**Diurnal rhythm**	**Low-dose suppression**	**High-dose suppression**	**Metyrapone test response**	**Plasma ACTH**
Normal	Normal	Yes	Yes	Yes	Yes	Normal
Cushing's disease	High	No	No	Yes	Yes	Increases
Tumor	High	No	No	No	No	Decreases
Non-ACTH-dependent hyperplasia	High	No	No	No	No	Decreases
Ectopic ACTH syndrome	High	No	No	No	No	Increases

[a] Low dose = 0.22 mg/10 kg for 2 days; high dose = 0.84 mg/10 kg for 3 days.

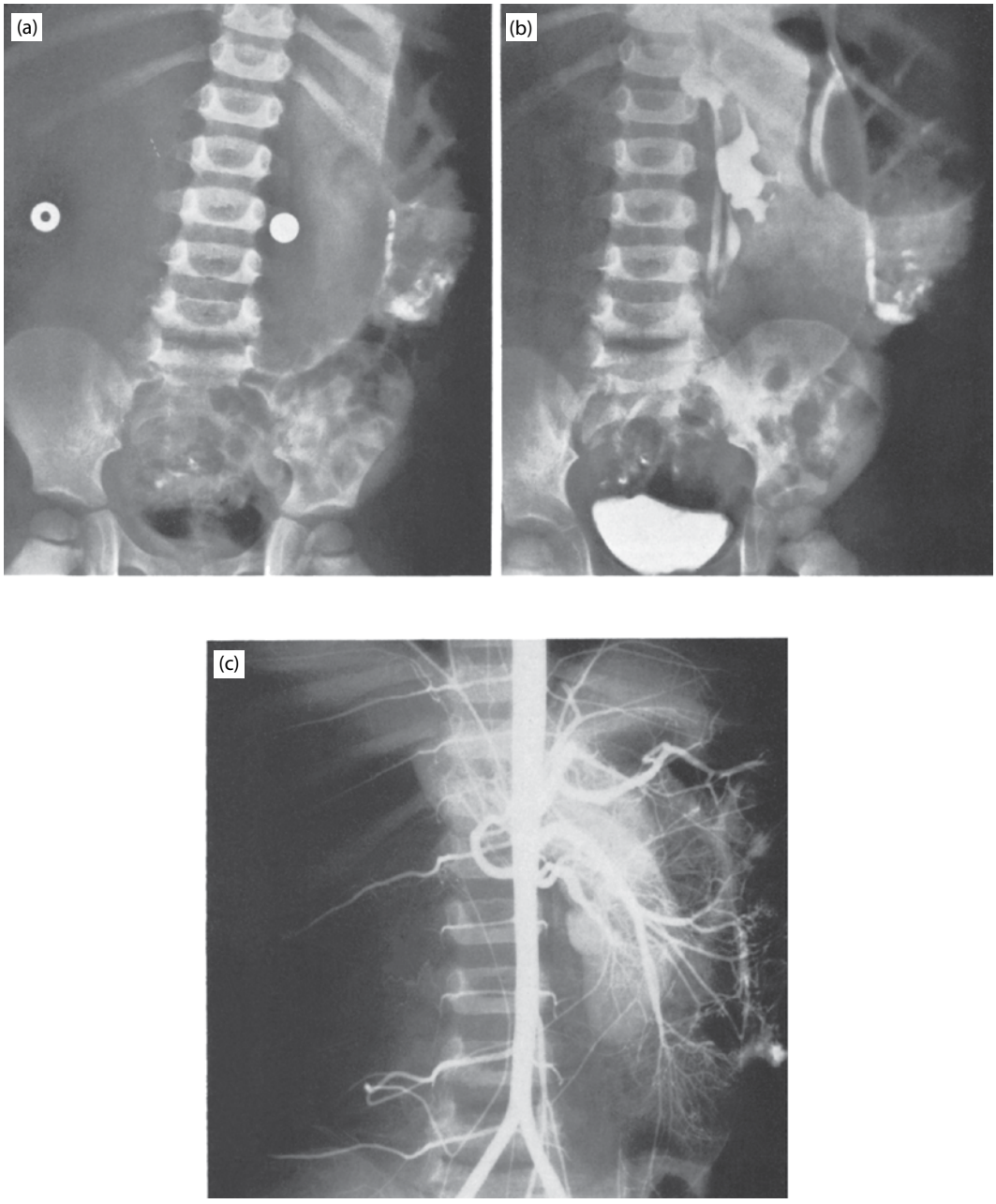

FIGURE 82.16 Retroperitoneal lipoma. (a) Abdominal film (kidney, ureter, and bladder) demonstrating a retroperitoneal mass obliterating the right psoas shadow and displacing the bowel to the left. (b) Excretory urogram showing the right kidney and ureter displaced across the midline to the left. Note the absence of hydronephrosis. (c) Aortogram shows displacement of the right renal artery. The right kidney is now superior to the left kidney. The absence of neovascularity suggests the benign nature of the tumor.

outlined in the previous section on benign ganglioneuromas, partial excision may be an appropriate surgical treatment.

LIPOMA

Retroperitoneal lipomas are usually benign, presenting as an abdominal mass in infants and young children (Figure 82.16). CT defines the characteristically low-density lesions. These are generally benign and well encapsulated. Local excision is the treatment of choice.

OTHER MALIGNANT RETROPERITONEAL TUMORS

Hodgkin's and non-Hodgkin's lymphomas may involve intra-abdominal viscera, including the urinary and gastrointestinal tracts. Lateral deviation of the ureters is the most common genitourinary feature; however, ureteral obstruction may be the primary presenting symptom. Ureteral catheterization may become necessary in advance of chemotherapy.

Liposarcoma

Liposarcoma is rare in children, being seen more often in the teenage years leading into young adulthood. If it is identified early, surgical excision may result in complete cure.

Fibrosarcoma

Fibrosarcoma may be difficult to distinguish from neurofibroma. These lesions also occur primarily in the extremities, although retroperitoneal sites may be seen.

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Section 7

Looking to the Future

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CHAPTER 83

Tissue Engineering for Pediatric Urology

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INTRODUCTION

Human organs are exposed to a variety of possible injuries from the time the fetus develops. Individuals may suffer from congenital disorders, cancer, trauma, infection, inflammation, iatrogenic injuries, or other conditions that may lead to organ damage or loss and necessitate eventual reconstruction or replacement. Whenever there is deficient organ function, replacement may be achieved with artificial organs or organ transplantation. These are flawed therapies, however, as artificial organs are not able to replace all physiologic functions and cannot fully integrate functionally into body systems, while organ transplantation is marred by donor shortages and immunologic rejection, and requires chronic and morbid medical therapy. In most cases, the replacement of lost or deficient tissues with functionally equivalent autologous tissues would improve the outcome for patients immensely. Tissue engineering therapies have been developed in order to achieve this goal.

The development of functional organ systems from the building blocks of cells, scaffolding, and growth factors is a Herculean task, however, as evidenced by the few successful tissue engineering technologies currently in clinical use. There have been successes, though, as seen by functioning autologous bioengineered tissues that have been implanted in humans—including trachea, blood vessels, pulmonary valves, endothelialized vascular stents, and urinary bladder.[1] An examination of the building blocks of tissue engineering strategies, as well the successful applications of these techniques in human clinical applications, provides an insight into the difficulties facing scientists as they seek to develop more complex bioengineered organs.

TISSUE ENGINEERING: STRATEGIES FOR TISSUE RECONSTITUTION

The field of regenerative medicine encompasses various areas of technology, such as tissue engineering, stem cells, and cloning. One of the major components of regenerative medicine, tissue engineering, follows the principles of cell transplantation, materials science, and engineering toward the development of biological substitutes that can restore and maintain normal function. Tissue engineering strategies generally fall into three categories: the use of acellular matrices (where matrices are used alone and which depend on the body's natural ability to regenerate for proper orientation and direction of new tissue growth), the use of simple cells, and the use of matrices combined with cells. The main obstacles that must be overcome for the clinical application of these strategies are localizing reliable, immunocompatible cell sources; developing biocompatible and functional scaffolding; and providing growth factors and vascularization for bioengineered organs.

Acellular tissue matrices are usually prepared by manufacturing artificial scaffolds, or by removing cellular components from tissues via mechanical and chemical manipulation to produce collagen-rich matrices.[2–5] These matrices tend to slowly degrade on implantation and are generally replaced by the extracellular matrix (ECM) proteins that are secreted by the ingrowing cells. Cells can be used in combination with scaffolds or injected as simple cell therapy, either with carriers (such as hydrogels) or alone.[6]

CELL SOURCES

When cells are used for tissue engineering, a small piece of donor tissue must be harvested and dissociated into individual cells. These cells are either implanted directly into the host or expanded in culture, attached to a support matrix, and then reimplanted into the host after expansion. The source of donor tissue can be heterologous (such as bovine), allogeneic (same species, different individual), or autologous. Ideally, both structural and functional tissue replacement will occur with minimal complications. The most preferred cells to use are autologous cells, where a biopsy of tissue is obtained from the host, the cells are dissociated and expanded in culture, and the expanded cells are implanted into the same host.[4,7–18] The use of autologous cells, although it may cause an inflammatory response, avoids rejection, and thus the deleterious side effects of immunosuppressive medications can be avoided.

One of the limitations of applying cell-based regenerative medicine techniques toward organ replacement has been the inherent difficulty of growing specific cell types in large quantities. Even when some organs, such as the liver, have a high regenerative capacity in vivo, cell

growth and expansion in vitro may be difficult. By studying the privileged sites for committed precursor cells in specific organs, as well as exploring the conditions that promote differentiation, one may be able to overcome the obstacles that could lead to cell expansion in vitro. For example, urothelial cells could be grown in the laboratory setting in the past, but only with limited expansion. Several protocols were developed over the last two decades that identified the undifferentiated cells, and kept them undifferentiated during their growth phase.[9,19–21] Using these methods of cell culture, it is now possible to expand a urothelial strain from a single specimen that initially covers a surface area of 1 cm^2 to one covering a surface area of 4202 m^2 (the equivalent area of one football field) within 8 weeks.[9] These studies indicated that it should be possible to collect autologous bladder cells from human patients, expand them in culture, and return them to the human donor in sufficient quantities for reconstructive purposes.[9,19,22–26] Major advances have been achieved within the last decade on the possible expansion of a variety of primary human cells, with specific techniques that make the use of autologous cells possible for clinical application.

A recent discovery may well influence cell sourcing for regenerative medicine strategies. A new type of interstitial cell, termed telocytes, has been isolated, and these cells have been found to be crucial to the process of evolution of progenitor cells toward mature development. Their architecture (tracks for migrations) and paracrine secretions (including microRNA) provide the environment for progenitor cell maturation. These cells have been found in many organs, including myocardium, and have been demonstrated to be crucial to neoangiogenesis following myocardial ischemia. These cells and their signals may hold clues to creating more appropriate milieus for precursor cell development and angiogenesis.[27]

An area of concern in the field of tissue engineering in the past was the source of cells for regeneration. The concept of creating engineered constructs involves initially obtaining cells for expansion from the diseased organ. A study recently showed that cultured neuropathic bladder smooth muscle cells possess and maintain different characteristics than normal smooth muscle cells in vitro, as demonstrated by growth assays, contractility, and adherence tests in vitro.[28] *However, when neuropathic smooth muscle cells were cultured in vitro, and seeded onto matrices and implanted in vivo, the tissue-engineered constructs showed the same properties as the tissues engineered with normal cells.*[29] It is known that genetically normal progenitor cells, which are the reservoirs for new cell formation, are programmed to give rise to normal tissue, regardless of whether the niche resides in either normal or diseased tissues. The stem cell niche and its role in normal tissue regeneration remains a fertile area of ongoing investigation.

In circumstances where source cell gene expression may be pathologically altered, gene-modifying techniques have been aggressively explored—including epigenetic therapies and gene transfer techniques (using viral vectors or polymer-based gene delivery). Although the precise control of new gene expression remains complex, the use of gene delivery in combination with varying cell populations may expand the cell sources available for regeneration.[27]

ALTERNATE CELL SOURCES

Stem Cells

Most current strategies for tissue engineering depend on a sample of autologous cells from the diseased organ of the host. However, for many patients with extensive end-stage organ failure, a tissue biopsy may not yield enough normal cells for expansion and transplantation. In other instances, primary autologous human cells cannot be expanded from a particular organ, such as the pancreas. In these situations, pluripotent human embryonic stem cells are envisioned as a viable source of cells, as they can serve as an alternative source of cells from which the desired tissue can be derived.[30]

Human embryonic stem cells exhibit two remarkable properties: the ability to proliferate in an undifferentiated, but pluripotent state (self-renew), and the ability to differentiate into many specialized cell types.[31] They can be isolated by immunosurgery from the inner cell mass of the embryo during the blastocyst stage (5 days postfertilization), and are usually grown on feeder layers consisting of mouse embryonic fibroblasts or human feeder cells.[32] More recent reports have shown that these cells can be grown without the use of a feeder layer,[33] and thus avoid the exposure of these human cells to mouse viruses and proteins. These cells have demonstrated longevity in culture by maintaining their undifferentiated state for at least 80 passages when grown using current published protocols.[34,35]

Human embryonic stem cells have been shown to differentiate into cells from all three embryonic germ layers in vitro. Skin and neurons have been formed, indicating ectodermal differentiation.[36–38] Blood, cardiac cells, cartilage, endothelial cells, and muscle have been formed, indicating mesodermal differentiation.[39–41] And pancreatic cells have been formed, indicating endodermal differentiation.[42] In addition, as further evidence of their pluripotency, embryonic stem cells can form embryoid bodies, which are cell aggregations that contain all three embryonic germ layers, while in culture, and can form teratomas in vivo.[43]

Adult stem cells have the advantage of avoiding the ethical issues associated with embryonic cells, and also, they do not transdifferentiate spontaneously to a malignant phenotype. The use of adult stem cells is limited for clinical therapy due to the difficulties encountered with cell expansion to large quantities.

Fetal stem cells derived from amniotic fluid and placentas have been recently described and represent a novel source of stem cells. The cells express markers consistent with human embryonic stem cells, such as OCT4 and SSEA-4, but do not form teratomas, and do not spontaneously transdifferentiate to a malignant phenotype. The cells are multipotent and are able to differentiate into all three germ layers. In addition, the cells have a high replicative potential and could be stored for future self-use, without the risks of rejection, and without ethical concerns.[44]

THERAPEUTIC CLONING

While there has been tremendous interest in the field of nuclear cloning since the birth of Dolly in 1997, the first successful nuclear transfer was reported more than 50 years ago by Briggs and King.[45] Cloned frogs,[45] which were the first vertebrates derived from nuclear transfer, were subsequently reported by Gurdon in 1962,[46] but the nuclei were derived from nonadult sources. In the past several years, tremendous advances in nuclear cloning technology have been reported, indicating the relative immaturity of the field. Dolly was not the first cloned mammal to be produced from adult cells; in fact, live lambs were produced in 1996 using nuclear transfer and differentiated epithelial cells derived from embryonic discs.[47] The significance of Dolly was that she was the first mammal to be derived from an adult somatic cell using nuclear transfer.[48] Since then, animals from several species have been grown using nuclear transfer technology, including cattle,[49] goats,[50,51] mice,[52] and pigs.[53]

Two types of nuclear cloning, reproductive cloning and therapeutic cloning, have been described, and a better understanding of the differences between the two types may help to alleviate some of the controversy that surrounds these technologies. Banned in most countries for human applications, reproductive cloning is used to generate an embryo that has genetic material identical to that of its cell source. This embryo can then be implanted into the uterus of a female to give rise to an infant that is a clone of the donor. On the other hand, therapeutic cloning is used to generate early-stage embryos that are explanted in culture to produce embryonic stem cell lines whose genetic material is identical to that of its source. These autologous stem cells have the potential to become almost any type of cell in the adult body, and thus would be useful in tissue and organ replacement applications.[54] Therefore, therapeutic cloning, which has also been called somatic cell nuclear transfer, may provide an alternative source of transplantable cells. According to data from the Centers for Disease Control, it has been estimated that approximately 3000 Americans die every day of diseases that could have been treated with stem cell–derived tissues.[34] With current allogeneic tissue transplantation protocols, rejection is a frequent complication because of immunologic incompatibility, and immunosuppressive drugs are usually administered to treat and hopefully prevent host versus graft disease.[55] The use of transplantable tissue and organs derived from therapeutic cloning may potentially lead to the avoidance of immune responses that typically are associated with transplantation of nonautologous tissues.[44]

While promising, somatic cell nuclear transfer technology has certain limitations that require further improvements before therapeutic cloning can be widely applied in replacement therapy. Currently, the efficiency of the overall cloning process is low. The majority of embryos derived from animal cloning do not survive after implantation.[56–58] In practical terms, multiple nuclear transfers must be performed in order to produce one live offspring for animal cloning applications. The potential for cloned embryos to grow into live offspring is between 0.5% and 18% for sheep, bovine, pigs, and mice.[59] However, greater success (80%) has been reported in cattle,[60] which may be in part due to the availability of advanced bovine supporting technologies, such as in vitro embryo production and embryo transfer, which have been developed for this species for agricultural purposes. To improve cloning efficiencies, further improvements are required in the multiple complex steps of nuclear transfer, such as enucleation and reconstruction, activation of oocytes, and cell cycle synchronization between donor cells and recipient oocytes, that will more readily produce viable sources of cells.

Furthermore, common abnormalities have been found in newborn clones if they survive to birth, including enlarged size with an enlarged placenta ("large-offspring syndrome");[61] respiratory distress; defects of the kidney, liver, heart, and brain;[62] obesity;[63] and premature death.[64] *These may be related to the epigenetics of the cloned cells, which involve the reversible modifications of the DNA or chromatin, while the original DNA (genetic) sequences remain intact.* Faulty epigenetic reprogramming in clones, where the DNA methylation patterns, histone modifications, and overall chromatin structure of the somatic nuclei are not being reprogrammed to an embryonic pattern of expression, may explain the above abnormalities.[54] Reactivation of key embryonic genes at the blastocyst stage is usually not present in embryos cloned from somatic cells, while embryos cloned from embryos consistently express early embryonic genes.[65,66] Proper epigenetic reprogramming to an embryonic state may help to improve the cloning efficiency and reduce the incidence of abnormal cloned cells.

BIOMATERIALS

For cell-based tissue engineering, once cells have been cultured and expanded, they are seeded onto a scaffold synthesized using the appropriate biomaterial. In tissue engineering, biomaterials replicate the biologic and mechanical function of the native ECM found in tissues in the body by serving as an artificial ECM. As a result, biomaterials provide a three-dimensional space for the cells to form into new tissues with appropriate structure and function, and also can allow for the delivery of cells and appropriate bioactive factors (e.g., cell adhesion peptides and growth factors) to desired sites in the body.[67] As the majority of mammalian cell types are anchorage dependent and will die if no cell adhesion substrate is available, biomaterials provide a cell adhesion substrate that can deliver cells to specific sites in the body with high loading efficiency. Biomaterials can also provide mechanical support against in vivo forces such that the predefined three-dimensional structure is maintained during tissue development. Furthermore, bioactive signals, such as cell adhesion peptides and growth factors, can be loaded along with cells to help regulate cellular function.

The ideal biomaterial should be biocompatible in that it is biodegradable and bioresorbable to support the replacement of normal tissue without inflammation. Incompatible materials are destined for an inflammatory or foreign body response that eventually leads to rejection

and/or necrosis. In addition, the degradation products, if produced, should be removed from the body via metabolic pathways at an adequate rate that keeps the concentration of these degradation products in the tissues at a tolerable level.[68] Furthermore, the biomaterial should provide an environment in which appropriate regulation of cell behavior (e.g., adhesion, proliferation, migration, and differentiation) can occur such that functional tissue can form. Cell behavior in the newly formed tissue has been shown to be regulated by multiple interactions of the cells with their microenvironment, including interactions with cell adhesion ligands[69] and with soluble growth factors. In addition, biomaterials provide temporary mechanical support that allows the tissue to grow in three dimensions while the cells undergo spatial tissue reorganization. The properly chosen biomaterial should allow the engineered tissue to maintain sufficient mechanical integrity to support itself in early development, while in late development, the properly chosen biomaterial should have begun degradation such that it does not hinder further tissue growth.[67]

Generally, three classes of biomaterials have been utilized for engineering tissues: naturally derived materials (e.g., collagen and alginate), acellular tissue matrices (e.g., bladder submucosa and small intestinal submucosa [SIS]), and synthetic polymers (e.g., polyglycolic acid [PGA], polylactic acid [PLA], and poly(lactic-co-glycolic acid) [PLGA]). These classes of biomaterials have been tested with respect to their biocompatibility.[70,71] Naturally derived materials and acellular tissue matrices have the potential advantage of biological recognition. However, synthetic polymers can be produced reproducibly on a large scale with controlled properties of their strength, degradation rate, and microstructure.

Collagen is the most abundant and ubiquitous structural protein in the body and may be readily purified from both animal and human tissues with an enzyme treatment and salt or acid extraction. Collagen implants degrade through a sequential attack by lysosomal enzymes. Controlling the density of the implant and the extent of intermolecular cross-linking can regulate the in vivo resorption rate. The lower the density, the greater the interstitial space and generally the larger the pores for cell infiltration, leading to a higher rate of implant degradation. Collagen contains cell adhesion domain sequences (e.g., RGD) that exhibit specific cellular interactions. This may assist in retaining the phenotype and activity of many types of cells, including fibroblasts[72] and chondrocytes.[73]

Alginate, a polysaccharide isolated from seaweed, has been used as an injectable cell delivery vehicle[74] and a cell immobilization matrix[75] owing to its gentle gelling properties in the presence of divalent ions, such as calcium. Alginate is relatively biocompatible and approved by the Food and Drug Administration (FDA) for human use as wound dressing material. Alginate is a family of copolymers of D-mannuronate and L-guluronate. The physical and mechanical properties of alginate gel are strongly correlated with the proportion and length of polyguluronate block in the alginate chains.[74]

Acellular tissue matrices are collagen-rich matrices prepared by removing cellular components from tissues.[2–5] The matrices are often prepared by mechanical and chemical manipulation of a segment of tissue. The matrices slowly degrade upon implantation and are replaced and remodeled by ECM proteins synthesized and secreted by transplanted or ingrown cells.

Polyesters of naturally occurring α-hydroxy acids, including PGA, PLA, and PLGA, are widely used in tissue engineering. These polymers have gained FDA approval for human use in a variety of applications, including sutures. The ester bonds in these polymers are hydrolytically labile, and these polymers degrade by nonenzymatic hydrolysis. The degradation products of PGA, PLA, and PLGA are nontoxic, natural metabolites and are eventually eliminated from the body in the form of carbon dioxide and water. The degradation rate of these polymers can be tailored from several weeks to several years by altering crystallinity, initial molecular weight, and the copolymer ratio of lactic to glycolic acid. Since these polymers are thermoplastics, they can be easily formed into a three-dimensional scaffold with a desired microstructure, gross shape, and dimension by various techniques, including molding, extrusion,[76] solvent casting, phase separation techniques, and gas foaming techniques.[77] Many applications in tissue engineering often require a scaffold with a high porosity and ratio of surface area to volume. Other biodegradable synthetic polymers, including poly(anhydrides) and poly(ortho-esters), can also be used to fabricate scaffolds for tissue engineering with controlled properties.[78]

A recently developed polymer, polyhedral oligomeric silsesquioxane/poly(carbonateurea) urethane (POSS-PCU), is a highly biocompatible nanocomposite that has demonstrated many of the ideal characteristics for tissue engineering numerous implants.[1]

Other advances in biomaterial engineering include the development of conducting polymers that may find roles in neural tissue engineering, and ionic polymer metal composites that can induce movement with appropriate stimulation, and therefore may serve roles in the development of artificial muscles or dynamic sensors.[1]

GROWTH FACTORS

A key component to scaffold function is the presence of the appropriate growth factors for cell growth and maturation. Growth factors may be produced by cells themselves (autocrine) or the surrounding environment (paracrine). Scientists have employed various strategies to enhance desirable growth factor production, in order to promote the cell growth and maturation needed for particular organ systems. Some investigators have attempted to influence cell growth factor production with gene therapy, by incorporating genes for growth factor transcription in the transplanted cells. Others have sought to simply inject the growth factors into the cells' milieu, but this method often results in rapid dissipation of the agents due to diffusion.[79]

A novel method of growth factor use in tissue engineering involves the incorporation of growth factors into carriers or cell scaffolds. The goals of these techniques are to provide localized and controlled release of the growth factors necessary for cell development. Extensive research is underway to define the exact combination of growth

factors needed for specific organ growth and maturation, with an emphasis on the use of these factors to induce more rapid cell development and differentiation, appropriate cell function and orientation, and ECM development and vascularization.[80]

In addition to the influence of growth factors, the simple topography of a scaffold has been demonstrated to greatly affect cell growth. For example, the shape of grooves in scaffolds can influence cell proliferation and cell alignment, and assist in cell differentiation.[1]

VASCULARIZATION

One of the restrictions of the engineering of tissues is that cells cannot be implanted in volumes exceeding 3 mm^3 because of the limitations of nutrition and gas exchange.[81] To achieve the goals of engineering large complex tissues, and possibly internal organs, vascularization of the regenerating cells is essential.

Three approaches have been used for vascularization of bioengineered tissue: (1) incorporation of angiogenic factors in the bioengineered tissue, (2) seeding ECM with other cell types in the bioengineered tissue, and (3) prevascularization of the matrix prior to cell seeding. Angiogenic growth factors may be incorporated into the bioengineered tissue prior to implantation, in order to attract host capillaries and enhance neovascularization of the implanted tissue. There are many obstacles to overcome before large entire tissue-engineered solid organs are produced. Recent developments in angiogenesis research may provide important knowledge and essential materials to accomplish this goal.

The modern strategies of neo-organ vascularization have investigated the aforementioned use of growth factors and cytokines such as vascular endothelial growth factor (VEGF), progenitor cells, biomaterials, or fabricated vessel conduits, or combinations of those techniques. Because tissue engineering is often required in the setting of severe tissue damage (such as following radiation for tumor therapy) and immediate oxygenation of a large construct may be needed (where neoangiogenesis may not be possible or rapid enough), the in vivo creation of arteriovenous loops has been favored, and the most efficacious vascularization of solid organs has been found to be accomplished with the anastomosis of prevascularized constructs in combination with the local and controlled release of angiogenic growth factors.[27]

CLINICAL APPLICATIONS

The assimilation of all these complex technologies into functional bioengineered organs is a complex task. By examining the early attempts at the application of tissue engineering for clinical use, the difficulties and challenges facing scientists in the future are more clearly delineated. The application of bioengineered organs for human use has been addressed in a logical fashion, beginning with the simplest organ systems (e.g., skin) and extending to hollow organs (e.g., bladder) and finally complex solid organs (e.g., kidneys).

Urethra

Different approaches have been suggested for the regeneration of urethral tissue. Woven PGA (Dexon®) meshes without cells have been used to reconstruct the urethra in dogs.[82,83] Furthermore, PGA has been used as a cell carrier to engineer tubular urothelium in vivo. SIS without cells and a homologous free graft of acellular urethral matrix were used as grafts for urethroplasty in rabbit models.[84,85]

Bladder-derived acellular collagen matrix has proven to be a suitable graft for repair of urethral defects, and the created neourethras showed normal urothelial lining and organized muscle bundles in the rabbit model.[5] The above results were confirmed clinically in a series of patients with a history of failed hypospadias repair wherein the urethral defects were repaired with human bladder acellular collagen matrices.[86]

The described techniques, using nonseeded acellular matrices, were applied experimentally and clinically in a successful manner for onlay urethral repairs. However, when tubularized urethral repairs were attempted experimentally, adequate functional urethral tissue regeneration was not achieved, and complications, predominantly graft contracture and stricture formation, were noticed). On the contrary, seeded tubularized collagen matrices have performed better in animal studies. In a rabbit model, urethroplasty was performed with tubularized collagen matrices seeded either with cells or without cells. The matrices seeded with autologous cells formed new tissue, which was histologically comparable to that of native urethra. The tubularized collagen matrices without cells, however, led to limited tissue development, fibrosis, and stricture formation. These findings were also confirmed clinically.[87]

Bladder

Currently, gastrointestinal segments are commonly used as tissues for bladder replacement or repair.[88,89] Because of the problems encountered with the use of gastrointestinal segments, numerous investigators have attempted alternative reconstructive procedures for bladder replacement or repair, such as the use of tissue expansion, seromuscular grafts, matrices for tissue regeneration, and tissue engineering with cell transplantation.[88]

Cell-seeded allogeneic acellular bladder matrices are one of the few strategies of bioengineered bladder replacement with human clinical applications. The early work with this technology was performed in dogs, where a group of experimental canines underwent a trigone-sparing cystectomy with closure of the trigone without a reconstructive procedure, or reconstruction with a nonseeded bladder-shaped biodegradable scaffold, or reconstruction using a bladder-shaped biodegradable scaffold that delivered seeded autologous urothelial cells and smooth muscle cells.[16]

The results were promising, with the cystectomy-only and nonseeded controls demonstrating decreased capacities and compliance compared with the preoperative values, while the cell-seeded tissue-engineered bladders showed increased capacity and compliance, with histology

depicting normal cellular organization, consisting of a trilayer of urothelium, submucosa, and muscle.[16]

Preliminary clinical trials for the application of this technology have been performed and have had promising results. Recently published data demonstrated that engineered autologous bladder tissue may be used to safely augment the bladder in children with end-stage bladder disease secondary to myelomeningocele.[90] In this study, seven patients, aged 4–19, with high pressure or poorly compliant bladders were selected as candidates for autologous augmentation cystoplasty. Bladder biopsies were obtained from each patient, and smooth muscle and urothelial cells were cultured, expanded, and seeded on composite scaffolds. Approximately 7 weeks after the biopsy, the autologously generated neobladders were used for bladder reconstruction with or without omental wrapping. At a mean follow-up of 46 months, the increase in bladder volume and compliance was greatest in the engineered bladders coated in the omental wrap. Bowel function returned promptly after surgery; there were no metabolic complications, stone formation, or mucous production; and renal function was preserved. In addition, engineered bladder biopsies demonstrated normal structural architecture and phenotype. Thus, this study provided good evidence in support of the use of engineered bladder tissue (created with autologous cells seeded on a composite scaffold, and wrapped in omentum following implantation), for patients in need of cystoplasty.

Ureter

Ureteral nonseeded matrices have been used as scaffolds for the growth of ureteral tissue in rats. The acellular matrices promoted the regeneration of the ureteral wall components.[91] Ureteral replacement with polytetrafluoroethylene (Teflon) grafts in dogs resulted in poor functional results.[92] Nonseeded ureteral collagen acellular matrices were tubularized and used to replace segments of canine ureters. The nonseeded acellular matrix tube was not able to successfully replace the resected segment of the ureter.[93]

Cell-seeded biodegradable polymer scaffolds have proved to be more successful in reconstruction of ureteral tissues. In one study, urothelial and smooth muscle cells isolated from bladders and expanded in vitro were seeded onto tubular PGA scaffolds and thereafter implanted subcutaneously into athymic mice. The urothelial cells proliferated to form a multilayered luminal lining, while the smooth muscle cells organized into multilayered structures surrounding the urothelial cells and pronounced angiogenesis was observed. The degradation of the polymer scaffolds resulted in formation of natural urothelial tissues. This approach was also used to replace ureters in dogs by transplantation of smooth muscle and urothelial cells on tubular polymeric scaffolds.[94]

Kidney

Solid organs are the most challenging to reconstruct by tissue engineering techniques because of their complex structure and function. Due to these complexities, some scientists approach the replacement of solid organ function, such as liver or kidney, with bioartificial approaches, combining the function of the organ's predominant cells with an artificial structure and organization.

An example of this strategy is extracorporeal renal replacement. Although dialysis is currently the most prevalent form of renal replacement therapy, the relatively high morbidity and mortality have spurred investigators to seek alternative solutions involving ex vivo systems. In an attempt to assess the viability and physiologic functionality of a cell-seeded device to replace the filtration, transport, metabolic, and endocrinologic functions of the kidney in acutely uremic dogs, a combination of a synthetic hemofiltration device and a renal tubular cell therapy device containing porcine renal tubules in an extracorporeal perfusion circuit was introduced. It was shown that levels of potassium and blood urea nitrogen (BUN) were controlled during treatment with the device. The fractional reabsorption of sodium and water was possible. Active transport of potassium, bicarbonate, and glucose and a gradual ability to excrete ammonia were observed. These results showed the technologic feasibility of an extracorporeal assist device that is reinforced by the use of proximal tubular cells.[95]

Using similar techniques, a tissue-engineered bioartificial kidney consisting of a conventional hemofiltration cartridge in series with a renal tubule assist device containing human renal proximal tubule cells was used in patients with acute renal failure (ARF) in the intensive care unit. The initial clinical experience with the bioartificial kidney and the renal tubule assist device suggests that renal tubule cell therapy may provide a dynamic and individualized treatment program as assessed by acute physiologic and biochemical indices.[96]

The ultimate goal of tissue engineering, however, is the growth of fully functional and fully integrated replacement organs. Thus, another approach toward the achievement of improved renal function involves the augmentation of renal tissue with kidney cell expansion in vitro and subsequent autologous transplantation. The feasibility of achieving renal cell growth, expansion, and in vivo reconstitution with the use of tissue engineering techniques has been explored.

Most recently, an attempt was made to harness the reconstitution of renal epithelial cells for the generation of functional nephron units. Renal cells were harvested and expanded in culture. The cells were seeded onto a tubular device constructed from a polycarbonate membrane, connected at one end with a Silastic catheter that terminated into a reservoir. The device was implanted in athymic mice. Histologic examination of the implanted devices over time revealed extensive vascularization with formation of glomeruli and highly organized tubule-like structures. Immunocytochemical staining confirmed the renal phenotype. Yellow fluid was collected from inside the implant, and the fluid retrieved was consistent with the makeup of dilute urine in its creatinine and uric acid concentrations.[6] Further studies have been performed showing the formation of renal structures in cows using nuclear transfer techniques.[97] Challenges await this technology, including the expansion of this system to larger, three-dimensional structures.

Uterus and Vagina

Congenital malformations, such as cloacal exstrophy and intersex disorders, may not have sufficient uterine tissue for future reproduction. The possibility of engineering functional uterine tissue, using autologous cells, was investigated.[98] For this reason, autologous rabbit uterine smooth muscle and epithelial cells were harvested and then cultured and expanded in vitro. Thereafter, the cells were seeded onto uterine-shaped biodegradable polymer scaffolds, which were consequently used for subtotal uterine tissue replacement. Six months after implantation, histological, immunohistochemical, and Western blot analyses confirmed the presence of normal uterine tissues. Biomechanical analyses and organ bath studies showed that the functional characteristics of these tissues were similar to those of normal uterine tissue.

Several pathologic conditions, including congenital malformations and malignancy, can adversely affect normal vaginal development or anatomy. Vaginal reconstruction is challenging due to the lack of native tissue. Vaginal epithelial and smooth muscle cells of female rabbits were harvested and expanded in culture. These cells were seeded onto biodegradable polymer scaffolds, and the cell-seeded constructs were then implanted into nude mice for up to 6 weeks. Immunohistochemical, histological, and Western blot analyses confirmed the presence of vaginal tissue phenotypes. Electrical field stimulation studies in the tissue-engineered constructs showed functional properties similar to those of normal vaginal tissue. When these constructs were used for autologous total vaginal replacement, functional vaginal structures were noted in the tissue-engineered specimens; however, implanting the non-cell-seeded structures resulted in stenotic structures.[99]

Testicle

Androgen substitution is necessary in patients with testicular dysfunction to allow normal somatic development. Testicular dysfunction is treated with periodic intramuscular injections of chemically modified testosterone and, more recently, transcutaneously with skin patch applications. However, long-term nonpulsatile testosterone therapy can cause multiple problems, including erythropoiesis and bone density changes.

For these reasons, a system was designed wherein Leydig cells were microencapsulated for controlled testosterone release. Purified Leydig cells were isolated and encapsulated in an alginate–poly-L-lysine solution. The encapsulated Leydig cells were injected into castrated animals, and serum testosterone was measured regularly. The animals were able to maintain their testosterone levels during long-term observation.[100] These studies suggest that it may be feasible in the future to use microencapsulated Leydig cells to replace or supplement testosterone in patients where anorchia or acquired testicular failure is present.

Penis

One of the major components of the phallus is corporal smooth muscle. The creation of autologous functional and structural corporal tissue de novo would be beneficial. In order to look at the functional parameters of the engineered corpora, acellular corporal collagen matrices were obtained from donor rabbit penis, and autologous corpus cavernosal smooth muscle and endothelial cells were harvested, expanded, and seeded on the matrices. The entire rabbit corpora were removed and replaced with the engineered scaffolds. The experimental corporal bodies demonstrated intact structural integrity by cavernosography and showed similar pressure by cavernosometry when compared with the normal controls. The control rabbits without cells failed to show normal erectile function throughout the study period. Mating activity in the animals with the engineered corpora appeared normal by 1 month after implantation. The presence of sperm was confirmed during mating, and was present in all the rabbits with the engineered corpora. The female rabbits mated with the animals implanted with engineered corpora and also conceived and delivered healthy pups. Animals implanted with the matrix alone were unable to demonstrate normal mating activity and failed to ejaculate into the vagina.[101]

Silicone is used as biomaterial for penile prostheses; however, biocompatibility remains a concern.[102,103] The appliance of a natural prosthesis composed of autologous cells may be advantageous. The feasibility of using autologous engineered cartilage rods in situ was investigated.[104] Chondrocytes were harvested from rabbit ears and grown and expanded in culture. The cells were then seeded onto biodegradable poly-L-lactic acid–coated PGA polymer rods and implanted into the corporal spaces of the rabbit penis. At retrieval, the presence of well-formed, milky-white cartilage structures within the corpora was noted at 1 month. The polymeric structures were fully degraded by 2 months. No evidence of erosion or infection in any of the implantation sites was observed. Further studies were performed to assess the long-term functionality of the cartilage penile rods in vivo. The animals can copulate and impregnate their female partners.

Engineered bulking agents in urology

Both vesicoureteral reflux and urinary incontinence are frequent conditions affecting the genitourinary system for which injectable bulking agents can be used for endoscopic treatment. The ideal substance for the treatment of reflux and incontinence should be easily injectable, nonantigenic, nonmigratory, volume preserving, and safe for use in humans. In clinical practice, hyaluronic acid, dextranomers, and collagen are commonly used.[105,106] Animal studies have shown that chondrocytes can be easily harvested, cultured together with alginate in vitro. The suspension can then be injected endoscopically, and the elastic cartilage subsequently formed is able to act as a bulking agent to correct vesicoureteral reflux without any evidence of obstruction.[107] The first human application of cell-based bulking agents occurred with the injection of chondrocytes for the correction of vesicoureteral reflux in children and for urinary incontinence in adults.[108,109]

The use of autologous smooth muscle cells was also explored for treatment of both urinary incontinence and vesicoureteral reflux.[110] The use of cultured myoblasts

for the injection treatment of stress urinary incontinence has also been investigated.[111,112] Additionally, the use of injectable muscle precursor cells has been investigated as a potential treatment of urinary incontinence due to irreversible urethral sphincter injury or maldevelopment.[113] A clinical trial involving the use of muscle-derived stem cells (MDSCs) to treat stress urinary incontinence has also been performed. Biopsies of skeletal muscle were obtained, and autologous myoblasts and fibroblasts were cultured. Under ultrasound guidance, myoblasts were injected into the rhabdosphincter, and fibroblasts together with collagen were injected into the submucosal space. One year following injection, the thickness and function of the rhabdosphincter had significantly increased and all patients were continent.[114]

Injectable muscle-based gene therapy and tissue engineering were combined to improve detrusor function in a bladder injury model, and may potentially be a novel treatment option for urinary incontinence.[115]

CONCLUSION

Tissue engineering efforts are currently being undertaken for almost every major type of tissue and organ within the body. Most of the effort expended to engineer these organs has occurred within the last decade. Tissue engineering techniques require a cell culture facility designed for human application. Personnel who have mastered the techniques of cell harvest, culture, and expansion, as well as polymer design, are essential for the successful application of this technology. Before these engineering techniques can be applied to humans, however, further studies need to be performed in many tissues.

In addition to the challenges mentioned above, there are numerous other hurdles that face the tissue engineers of tomorrow. For example, physiologically accurate bioreactors must be developed and refined if complex organs are to be grown and functionalized prior to implantation in humans. Also, a refinement in the approaches to tissue engineering must be achieved, as scientists explore whether preengineered, functional bioengineered replacement organs must be produced to repair tissue function, or whether the goal of tissue engineering should be to use simple biomaterials, cells, or growth factors to induce the repair or regrowth of these damaged organs.

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CHAPTER
84

Study Designs and Hierarchy of Evidence

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INTRODUCTION

In this chapter, the different types of research designs, with their potential advantages and limitations, are presented. Understanding these issues is essential to determining the strength of the evidence behind study results. Common hierarchies of different study designs in evidence-based medicine are reviewed. A system for grading the quality of evidence is also provided.

Evidence-based practice involves finding the available evidence, assessing its validity, and then using the strongest available evidence in conjunction with clinical judgment to inform decisions regarding patient care.

The hierarchy of evidence places systematic reviews and randomized controlled trials (RCTs) as the highest levels of evidence, whereas case reports and expert opinion are the lowest (Figure 84.1). Due to the intrinsic particularities of the pediatric urology field, it is useful to think of the various study designs not as a hierarchy, but as categories of evidence where the strongest, most practical, and ethical design should be used. Furthermore, the quality of each individual study should be assessed for strengths and weaknesses by checking the methodological safeguards against bias that are relevant to each particular study design.

RESEARCH DESIGN

Clinical research can be experimental or observational. Observational studies can identify an association between two variables, but cannot establish a cause-and-effect relationship. To address the question of causation, RCTs are the preferred choice.[1] In such type of trials, the intervention is under the control of the investigator, whereas in observational studies, the researcher observes patients at a point in time (cross-sectional studies) or over time (longitudinal studies). If the observations are made by looking forward and gathering new data, the study is prospective; if the event of interest has already occurred, the study is retrospective.

EXPERIMENTAL STUDIES

When conducting an experimental study, the allocation of interventions to individuals is under the control of the investigator and thus can be randomized. Experimental studies can be either controlled (with a comparison group) or uncontrolled. Uncontrolled studies provide weaker evidence, and they are typically performed early in an area of research to explore the safety of a new intervention or to gather baseline data for planning more definitive trials.[2] Controlled experimental studies or RCTs are the gold standard by which all clinical research is judged.

RANDOMIZED CONTROLLED TRIALS

The fact that randomization keeps study groups as similar as possible from the outset, together with other methodological safeguards against bias, such as blinding and allocation concealment, makes RCTs the best study design to minimize bias. "Bias is any factor or process that deviates the results or conclusions of the study away from the truth, causing either over or underestimation of the effects of an intervention."[1]

In clinical trials, unknown genetic, environmental, or psychosocial factors may affect the outcome of interest. Randomization, if done properly, reduces the risk that these unknown factors will be unbalanced between study groups. Allocation concealment can be achieved by using opaque envelopes, randomization tables, or computer-generated sequences. Dates of birth (even or odd), chart numbers, or any other type of alternating sequence is inappropriate because research personnel may be able, either directly or indirectly, to guess the randomization sequence. Although sometimes called pseudo- or quasi-randomized trials, these studies are considered nonrandomized.

The vast majority of surgical trials are open trials because both surgeons and patients are aware of the type of intervention being applied. Nevertheless, three other groups or individuals can and should be blinded whenever possible: outcome assessors, data analysts, and investigators who write trial results.[3] In order to preserve that, the allocation code is not broken until these components are completed. Although blinding of statisticians is a common practice, blinding of investigators writing the report is rarely done. The use of sham therapy in surgical trials (to blind patients) has been a long-debated issue due to ethical concerns.[4]

Evidence has shown that surgical interventions, especially when performed to reduce subjective symptoms such as pain, may be associated with a pronounced placebo

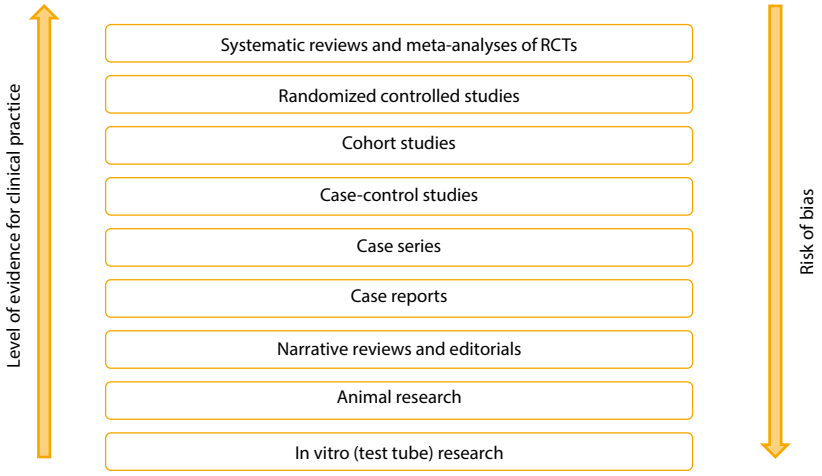


FIGURE 84.1 Hierarchy of evidence for clinical research.

effect.[5] A recent trial by Moseley and colleagues randomized 180 patients with osteoarthritis of the knee to receive arthroscopic debridement, arthroscopic lavage, or sham surgery. The investigators found that although both active therapies produced clinical benefit, neither was statically superior to the sham procedure.[6]

RCTs are not appropriate or feasible for all surgical interventions. It has been estimated that nearly 60% of surgical research questions could not be answered by an RCT, even in ideal clinical circumstances.[7] Furthermore, even when an RCT is appropriate, choosing the trial design can be challenging, as each one has its strengths and limitations.

Designing an RCT is not an easy task, especially when it involves thousands of patients. Herein, we present two reasons why it is necessary to have large RCTs in order to produce reliable results. First, the pathophysiology of most diseases is multifactorial, and given that most interventions target just one or two risk factors, it is unlikely that any particular intervention will have more than a moderate-sized treatment effect, or sometimes no effect if many confounders or biases are present.[8]

The second reason why we need large RCTs relates to a common error in interpreting the statistical significance of trial results, despite the size of the study and number of events.[8] Consider two hypothetical RCTs, each evaluating the effects of cranberry juice versus placebo in patients at risk of urinary tract infection (UTI). Both trials use identical high-quality methodology. The first trial randomizes 200 patients to receive cranberry juice and 200 to receive placebo, and fewer patients assigned to get cranberry juice develop a UTI (2 vs. 18 patients, $p = 0.02$). The second trial randomizes 8000 participants to receive cranberry juice and 8000 to receive placebo, and fewer participants receiving cranberry juice get a UTI (400 vs. 500 patients, $p = 0.02$). Given that both trials used the same high-quality methodology and achieved the same level of statistical significance, one would assume that we should view both results with similar confidence, but this should not be the case. Although the results have the same probability of representing a true finding (same p values), there is a substantial difference in the fragility of those p values. If only four events were added to the treatment group in the first trial, the p value would become 0.13. In contrast, adding two events to the treatment group in the second trial results in no meaningful impact on the p value, which would remain 0.02. Therefore, large trials are needed to ensure reliable estimates of treatment effects (Tables 84.1 and 84.2).

TYPES OF RANDOMIZED CONTROLLED TRIALS

Parallel Trials

Most RCTs make use of a parallel design, in which participants are randomized to two or more groups of equal size and each group is exposed to a different intervention. Parallel trials with more than one treatment arm (matched to a control arm) provide an opportunity to study multiple interventions; however, this also demands larger sample sizes to ensure that such trials are adequately powered to detect clinically important differences between interventions (Figure 84.2).[9]

Crossover Trials

A crossover trial design ensures that each study participant will receive all study interventions; however, the order in which they receive the interventions is random. As such, each participant acts as his or her own control, and individual patient characteristics that may influence response are therefore accounted for. Crossover trials produce within-patient

TABLE 84.1 Results from hypothetical set of trials

Trial 1			
Outcome	Treatment A ($n = 200$)	Placebo ($n = 200$)	p Value
UTI	2	18	0.02
Trial 2			
Outcome	Treatment B ($n = 8000$)	Placebo ($n = 8000$)	p Value
UTI	400	500	0.02

TABLE 84.2 Results demonstrating fragility of results in a small trial

Trial 1			
Outcome	Treatment A	Placebo	*p* Value
	(*n* = 200)	(*n* = 200)	
UTI	6	18	0.13
Trial 2			
Outcome	Treatment B	Placebo	*p* Value
	(*n* = 8000)	(*n* = 8000)	
UTI	404	500	0.02

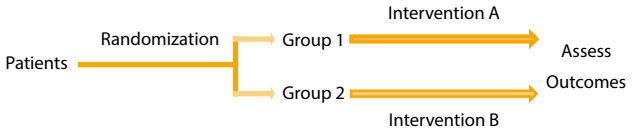


FIGURE 84.2 Parallel design RCT.

comparisons, and thus require fewer subjects than parallel trials to produce statistically significant results.[9]

On the other hand, interactions between interventions may occur with crossover trials, which may interfere with the sample size calculation. Interactions are more common when interventions have similar mechanisms of action, occurring when the effect of one intervention influences the other. For example, in the case of a negative interaction in which the overall effect of individual interventions is reduced when they are provided together, the sample size will need to be increased to detect the same clinically important difference as if there was no interaction.[9]

Factorial Design Trials

A factorial design RCT allows interventions to be evaluated both individually and in combination with one another. Therefore, two or more hypotheses can be explored in one experiment and the effect of combination therapy can be assessed. For example, in an RCT using a 2 × 2 factorial design, participants are allocated to one of four possible combinations: (1) treatment A, (2) treatment B, (3) treatment A and B, or (4) no treatment (Figure 84.3).[9]

n-of-1 Trials

A criticism of the aforementioned RCT designs is that they may provide good information on treatment outcome

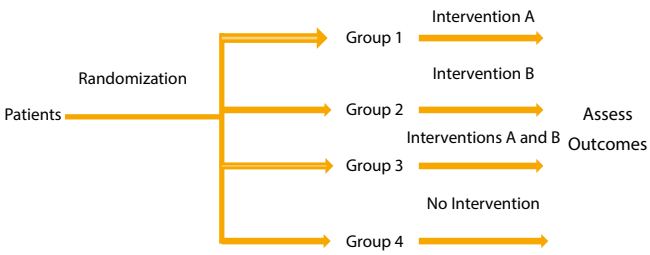


FIGURE 84.3 Factorial design RCT.

for the average patient, but are poorly equipped to provide individual-specific clinical information. RCTs that include only one patient are possible, and require limited resources. Such *n*-of-1 studies are conducted by systematically varying the management of a patient's illness during a series of treatment periods (alternating between experimental and control interventions) to confirm the effectiveness of treatment in that individual patient.[10] The number of pairs of interventions often varies from two to seven. This number is not prespecified, and the clinician and the patient can decide to stop the trial whenever it becomes clear that important differences between interventions have or have not been observed.

Observational Studies

As stated previously, RCTs may not be necessarily appropriate, ethical, or feasible in all situations. In general, questions of therapy are best answered by RCTs (or meta-analyses of RCTs, if available), whereas questions of diagnosis and prognosis may be best addressed by observational studies. Observational studies, which are frequently undertaken in surgery, provide weaker empirical evidence when compared with experimental studies because they are more prone to confounding and bias. Cohort and case-control studies both have been shown to exaggerate treatment effect estimates by up to 150% or reduce the actual effectiveness by up to 90%.[2]

To a large extent, the type of observational study done depends on the prevalence of the disease or condition and on issues related to human resources and costs. Usually, several methods of answering a research question are possible, and the strongest design should be used.

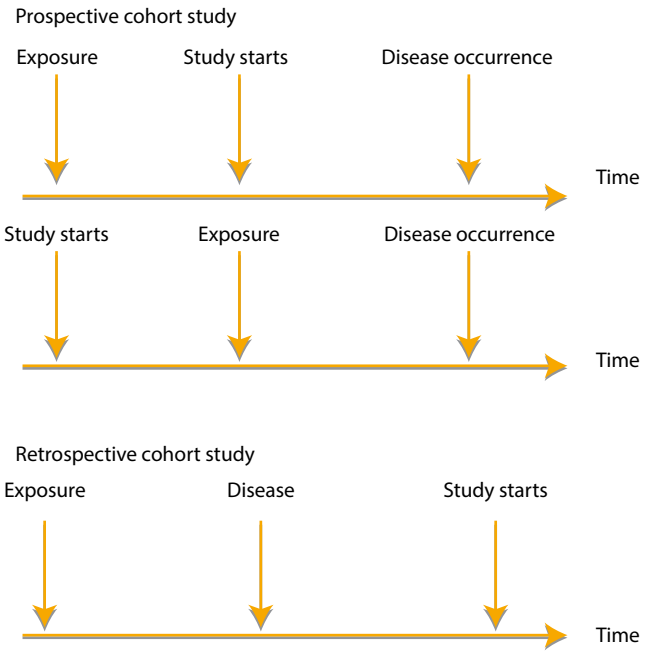
TYPES OF OBSERVATIONAL STUDIES

Cohort (Incidence) Study

In a cohort study, it is known at the outset whether people have been exposed to a treatment or possible causal agent (i.e., a type of trauma, surgical procedure, or drug), and patients are divided into groups or cohorts (exposed vs. nonexposed) on this basis. They are then followed forward in time (prospectively) for years or even decades to see how many in each group develop a particular outcome. These studies are usually less expensive and easier to administer than RCTs. They may also be ethically more acceptable because a potentially beneficial treatment is not withheld, and conversely, a possibly harmful treatment is not given. Cohort studies are susceptible to bias by having different loss to follow up numbers and lack o control over risk assignment. The major disadvantage is that one can never be sure that the cohorts were well matched for prognostic factors and there were no other confounding factors.[9]

A variation of a cohort study is a longitudinal study in which there is only one group. This group is composed of individuals who have a positive screening test or who have all been diagnosed with a disease in an early stage. Patients are then followed and evaluated on a repeated

basis to assess the development of the disease or for measurement of particular outcomes.[9]



Case-Control Study

This is a retrospective observational study in which the proportion of cases with the potential risk factor is compared with the proportion of controls (individuals without the disease or event) with the same risk factor. This is a relatively quick and inexpensive study and is often the best design for rare disorders or when the lag time between exposure and outcome is long. As with cohort studies, case-control studies are vulnerable to unmeasured confounding factors. Cases and controls must have had an equal likelihood of developing the disease under investigation in their baseline preexposure states.[9]

To understand the phenomenon of "confounding," one needs to consider the potential relation between an exposure (e.g., novel surgical technique) and an outcome (e.g., revision surgery or postoperative infection). The term *confounding* refers to a situation when one finds a spurious association or misses a true association between an exposure variable and an outcome variable as a result of a third factor or group of factors referred to as confounding variables.[11]

Therefore, factors that are linked to exposure and outcome are referred to as confounders. The impact of these factors must be assessed and addressed in the controls by matching members of the treatment and control groups on known confounding variables. Confounding is essentially an intrinsic limitation of observational studies (e.g., cohort studies and case-control studies) but is usually well addressed by large and well-designed RCTs. Nevertheless, small RCTs can occasionally run into problems with confounding simply owing to chance if their treatment groups are unbalanced with respect to participants' baseline characteristics.[11]

Confounding can be dealt with at the stage of study design (before collecting the data) or at the stage of data analysis (after collecting the data).[12] The commonly used methods to control for confounding factors and improve the internal validity of a study are randomization, restriction, matching, stratification, multivariable regression analysis, and propensity score analysis.[12]

Cross-Sectional (Prevalence) Studies

A cross-sectional study is a descriptive study of the relationship between an outcome (disease or trauma) and other factors. It usually takes a snapshot of a defined population at a specific point in time. Cross-sectional studies are effective in determining the prevalence of a disease or event (the proportion of the population that has the outcome of interest at a particular point in time) and the coexistence of associated variables. They do not give us information about the disease or event incidence (the proportion of the population that gets the outcome of interest over a specific period of time). Although these studies are relatively easy and inexpensive to carry out, a major limitation is that accurate reporting of the exposure and/or outcome of interest may depend on patients' recall of past events.[9]

Case Reports and Case Series

Case reports and case series are often used to describe a rare disorder or a novel aspect of a less rare condition, a new treatment or innovation, or adverse effects of an intervention. They often provide a great amount of information, which cannot be conveyed in a trial. The description of cases may alert surgeons to important new problems and then allow hypotheses to be generated, leading to focused studies of better design. Case reports and case series are of little use in guiding clinical practice because isolated observations are collected in an uncontrolled, unsystematic manner and the information gained cannot be generalized to a larger group of patients.[9]

Systematic Reviews and Meta-Analysis

Relying on single trials to make important clinical decisions, especially when the result is a change in practice, is often troublesome. Because the numbers of patients needed to detect small to moderate differences for clinically important outcomes may not be found in single studies, definitive answers can only be obtained by conducting well-designed large trials.

When the information from all relevant trials addressing the same question is combined using well-established, rigorous methodology, the result is a systematic review. Systematic reviews are reviews that incorporate strategies to minimize bias by having clearly formulated research questions, predefined inclusion and exclusion criteria, and explicit methodology to identify, select, and critically appraise studies.[13] These key characteristics of systematic reviews set them apart from traditional narrative reviews. The main differences between narrative and systematic reviews are summarized in Table 84.3.[14]

TABLE 84.3 Differences between narrative and systematic reviews

	Traditional review	Systematic review
Question	Often broad in scope	Focused question
Sources/search	Not usually specified, potentially biased	Comprehensive sources and explicit search strategy
Selection	Rarely specified, potentially biased	Criterion-based selection, uniformly applied
Appraisal	Variable	Rigorous critical appraisal, uniformly applied
Synthesis	Often a qualitative summary	Quantitative when appropriate
Inferences	Sometimes evidence based	Evidence based

Source: Adapted from Cook DJ et al. *Ann Intern Med*. 1997;126(5):376–80.

A systematic review may not necessarily include a meta-analysis, which can be defined as the statistical pooling of data from individual studies to create a single treatment effect estimate (pooled estimates of effects). In a meta-analysis, combining individual studies of small sample size increases statistical power (by increasing the total sample size of the study) and generates more precise effect estimates for that particular intervention under investigation. Usually, meta-analysis is the final step of a systematic review, and should only be performed when the variation of treatment effects between studies is small (low heterogeneity), allowing their pooling into a single estimate.[13]

When properly conducted, systematic reviews and meta-analyses of RCTs are ranked high in the hierarchy of evidence and may serve as the foundation for evidence-based practice guidelines, helping clinicians, researchers, and policy makers with a synthesis of the fast-growing literature in the field.[9]

Nevertheless, like any other research study, particularly one that is observational and retrospective, systematic reviews and meta-analyses can be subjected to systematic (bias) and random (chance) errors due to their own limitations.[15] These intrinsic limitations may originate from poor quality of included articles, heterogeneity between studies, and the presence of publication and outcome reporting biases.[16] Therefore, the validity and applicability of any systematic review depends mainly on the quality of the included studies and on how the review was carried out.[15]

Hierarchy of Research Studies

A hierarchy of research study design constitutes one of the core principles of evidence based medicine. In addition it is necessary to classify the available literature into levels of evidence to allow for clear communication among healthcare providers.

The incorporation of the levels of evidence into pediatric urology practice requires an understanding of what constitutes high- versus low-quality studies. For instance, a case report describing a surgical procedure makes one less certain about the effectiveness of that particular intervention when compared with evidence derived from a meta-analysis of multiple large, high-quality RCTs.[17] To acknowledge these quality issues, which are also linked to the amount of confidence one puts in research results, the Oxford Centre for Evidence-Based Medicine[18] has created a hierarchy of evidence to assist clinicians with their clinical decisions. Consequently, the level of confidence in the results is greatest when systematic error or bias is low.[17]

Several hierarchies of evidence and grading systems exist, and they may vary according to the type of study: therapeutic, prognostic, diagnostic, economic, and decision analyses. In most cases, the level of evidence and grading system adopted from the Oxford Centre for Evidence-Based Medicine has been implemented (Table 84.4).[18] For the purpose of this chapter, levels of evidence for therapy are discussed.

Common Hierarchies of Study Design for Treatment Studies

Therapeutic studies investigate the results of a treatment or intervention. The simplest hierarchy of an evidence system involves only looking at the study design, not the study quality. For instance, studies evaluating a

TABLE 84.4 Levels of evidence for therapeutic studies

Level of evidence	Therapeutic studies: Investigating the results of treatment
Level I	High-quality RCT with statistically significant difference or no statistically significant difference, but narrow confidence intervals
	Systematic review of level I RCTs (and study results were homogeneous)
Level II	Lesser-quality RCT (e.g., <80% follow-up, no blinding, or improper randomization)
	Prospective comparative study
	Systematic review of level II studies or level I studies with inconsistent results
Level III	Case-control study
	Retrospective comparative study
	Systematic review of level III studies
Level IV	Case series
Level V	Expert opinion

therapy, such as a novel surgical procedure or medication, commonly use the following hierarchy of evidence in descending order:

- Meta-analysis and systematic reviews of RCTs
- Randomized controlled trials
- Cohort studies
- Case-control studies
- Case reports
- Narrative reviews and editorials (expert opinions)
- Animal research
- In vitro research

This ranking has an evolutionary order, moving from simple observational methods at the bottom of the list through increasingly sophisticated and statistically refined methodologies at the top. In other words, as the research design becomes more rigorous, the quality of evidence increases, and the chance of bias decreases.[17] The RCT, by nature of randomization, has the ability to reduce selection bias.[19] This is extremely important, as bias can interfere with the outcome of a study, leading to over- or underestimation of treatment effects.[19] Randomization helps to control for both known and unknown prognostic factors in the groups under study, yielding a more accurate estimation of the truth.[19] On the other hand, observational studies are more prone to bias because investigators cannot adjust for all prognostic factors, especially the unknown ones.

Similar grading systems have been proposed. The main difference of their ranking is that they place the *n*-of-1 RCT at the top of the hierarchy of evidence, as displayed in Table 84.5. The reason for that is that the *n*-of-1 RCT provides clinical evidence on treatment outcome for that particular individual, as opposed to general information for the average patient.[20]

The levels of evidence table proposed by the Oxford Centre for Evidence-Based Medicine (Table 84.4) takes into consideration study design and methodological quality of the trials.[18]

High-quality RCTs with a statistically significant difference or no statistically significant difference, but narrow confidence intervals, and systematic reviews of level I RCTs with homogenous study results are classified as level I evidence.[9]

When assessing the quality of a systematic review or meta-analysis, it is necessary to look at the study design and quality of the included trials. Meta-analyses of RCTs combine data from individual studies by pooling them into a single estimate of treatment effect, increasing the sample size, and thereby the study power.[21]

TABLE 84.5 Hierarchy of study design

n-of-1 RCT
Systematic review of RCTs
Single RCTs
Systematic review of observational studies addressing patient-important outcomes
Single observational study addressing patient-important outcomes
Expert opinion

Lower-quality RCTs (e.g., <80% patient follow-up, lack of blinding, or improper randomization), prospective cohort studies, and systematic reviews of level II studies or level I studies with heterogeneous results are considered to be level II evidence. The prospective cohort study includes two groups of patients, one that received the intervention of interest and one that did not. Both groups are followed over time, and the outcomes are assessed and compared. Due to its prospective nature, data collection and follow-up are complete and accurate.[21]

Level III evidence includes the case-control study and systematic reviews of level III studies. The case-control study starts with a group that has the outcome of interest and looks back at other similar individuals to see what factors may have been present in the study group that may be associated with the outcome. Case-control studies are retrospective in nature and are prone to bias. Most retrospective studies have potential for bias because missing data and incomplete follow-up are often encountered.[21]

Case series are classified as level IV evidence. Case series are retrospective in nature and have no comparison group. They provide the outcome for only one group in the population, usually those who received the intervention, and the potential for bias is high, especially when there is incomplete data collection or patient follow-up. Because these studies are typically single-center or single-surgeon initiatives, the generalizability of the results is also limited.[9] Results of case series need to be interpreted cautiously.

Although the aforementioned hierarchy of study design and levels of evidence may vary, the premise is similar among the hierarchies, with high-quality RCTs at the top of the lists, followed by observational studies in the middle, and physiologic studies and unsystematic clinical observations at the bottom. Inferences may be very strong if results come from a systematic review of methodologically sound RCTs with homogeneous results.[19] Nevertheless, inferences should be weaker if only a single RCT is being considered, unless it is very large and the investigators have enrolled a diverse patient population.[19] Because observational studies may under- or overestimate treatment effects in an unpredictable manner, their results are far less trustworthy than those of RCTs.[9]

Grades of Recommendation

Assessing the quality of a study in relation to levels of evidence is extremely important when developing grades of recommendation. A grade of recommendation can only be developed after a thorough systematic review of the literature and, in many cases, after discussion with content experts.[22] When developing grades of recommendation, it is extremely important to place more weight on studies that are high on the hierarchy of evidence and have high methodological quality.[22]

In contrast, less weight should be given to studies that are low on the hierarchy of evidence and of lower methodological quality. The GRADE (Grading of Recommendation Assessment, Development, and Evaluation) Working Group suggests a system for grading the quality of the evidence obtained from a thorough systematic review (Table 84.6).[22]

TABLE 84.6 Criteria for assigning the grades of evidence

Types of evidence
Study design
Randomized trial = High quality
Quasi-randomized trial = Moderate quality
Observational study = Low quality
Any other evidence = Very low quality
Decrease grade if
Serious (–1) or very serious (–2) limitation to study quality
Important inconsistency (–1) Some (–1) or major (–2) uncertainty about directness Imprecise or sparse data (–1) High probability of reporting bias (–1)
Increase grade if
Strong evidence of association-significant relative risk of >2 (0.5) based on consistent evidence from two or more observational studies, with no plausible confounders (+1)
Very strong evidence of association-significant relative risk of >5 (0.2) based on direct evidence with no major threats to validity (+2) Evidence of dose–response gradient (+1) All plausible confounders would have reduced the effect (+1)

Source: Adapted from Atkin D et al. *BMJ* 2004;328:1490. Reprinted with permission.

This grading system should be applied to all outcomes of interest. Once the total evidence has been graded, a recommendation for treatment is then made.[22] The GRADE Working Group suggests that four areas should be considered when making a recommendation for treatment:[9]

1. What are the benefits versus the harm? Are there clear benefits to an intervention, or is there more harm as a result?
2. What is the quality of evidence?
3. Are there modifying factors affecting the clinical setting, such as proximity of qualified persons able to carry out the intervention?
4. What is the baseline risk for the potential population being treated?

Once all the factors have been considered, the recommendation should be placed into one of four categories:[22]

- Do it
- Probably do it
- Probably don't do it
- Don't do it

The grades of "do it" or "don't do it" are defined as a judgment that most well-informed people would make, and the grades of "probably do it" and "probably don't do it" are defined as a judgment that the majority of well-informed people would make, but a substantial minority would not.[22] The development of the grades of recommendation based on the GRADE Working Group system gives some one the tools to convey the best-available evidence to patients, as well as to help busy clinicians get connected with the most current evidence in the field.

Although RCTs provide the highest quality of evidence, evidence-based medicine is not the science of RCTs, thus neglecting other study designs. Evidence-based medicine explicitly acknowledges that a large body of what is called "state-of-the-art evidence" is derived from observational studies, mainly because higher-quality evidence is often not available, as is usually the case in many areas of pediatric urology.[23] In our field, few high-quality RCTs have been conducted evaluating existing surgical treatments.[3,23] Therefore, pediatric urologists are frequently forced to look for lower-quality evidence. The practice and application of evidence-based medicine requires an understanding of types of research design and critical evaluation of study methodology.

Nevertheless, this hierarchy is not absolute. If treatment effects are sufficiently large and consistent in observational studies, they may provide more compelling evidence than most small RCTs.[19] At the same time, instances in which results from an RCT contradict consistent results from observational studies reinforce the need for caution.

Observational Studies

As opposed to experiential studies that include random allocation of patients to certain interventions, in observational studies, a group (single cohort = case series) or multiple groups (multiple cohorts) are followed over time and assessed for the development of an outcome. Cohort studies can include historical controls or ideally involve a concurrent selection of controls.[9]

Case-control studies, in which the compared groups are defined based on the outcome, are also included under the umbrella of observational designs. Cohort studies can be prospective or retrospective, whereas a case-control study, by nature of the design, is always retrospective.[9]

Experimental versus Observational Study Design

Ongoing debate exists on whether the results of observational studies are consistent with those derived from RCTs. Clearly, the gold standard for comparing two interventions is an RCT. RCTs are considered experimental studies, whereas nonrandomized studies fall into the observational design category. The purpose of randomization is to balance known and unknown prognostic factors that may influence the outcome. Consequently, if outcome differences are observed in the groups being compared, this difference can be attributed to the intervention under study. Although some techniques exist to deal with known prognostic factors in observational studies, randomization is the only method capable of balancing all prognostic factors in the groups under comparison. Whenever an imbalance in prognostic factors between groups is noted, results will be biased toward one of the interventions under investigation.[9]

If data from RCTs are less prone to bias, should we rely on RCT data only and not trust observational studies? First and most importantly, not all research questions can be answered by a clinical trial or need to be answered by a clinical trial. Evaluating the outcome of multiple prognostic factors and their interaction on an outcome of interest,

for example, the influence of patient age at bladder closure, gender, comorbidities, osteotomies, and type of treatment on bladder exstrophy outcome, cannot be studied with an RCT design. This would require a prospective cohort study involving many centers and for many years. Second, in some situations, an RCT design might be possible but not feasible, for example, when looking at rare outcomes or outcomes that take too long to develop, such as end-stage renal disease in boys with posterior urethral valves. Case-control studies might be more appropriate for those conditions. However, in many cases, RCTs, as well as cohort studies, can be created to answer a specific research question, for example, compare two different surgical techniques for proximal hypospadias. Although RCTs are preferable due to their reduced risk of bias, they also have disadvantages: RCTs can be extremely expensive, and their generalizability is often limited because they are usually performed in large university centers, as opposed to small community-based hospitals. Available resources and surgeons' expertise may differ in both settings; therefore, results based on data from large university centers might not be generalizable to small community hospitals. Furthermore, in RCTs, groups are deliberately balanced to evaluate the effect of a single aspect on the outcome of interest, whereas in the real world, a particular treatment effect may be caused by a combination of factors. Thus, outcomes of an intervention in daily clinical practice (real life) may be different from those reported in RCTs.[9]

Criticisms of observational studies are largely based on the nonrandom allocation of patients to experimental and control groups, thus resulting in biases. Unrecognized confounding factors, which are never accounted for in observational studies, may distort results by over- or underestimating treatment effects. Consequently, these studies have a higher potential of being unsystematic and the recommendations derived from them are much weaker.

There continues to be a debate about the validity of data derived from observational studies. Evidence suggests that results derived from high-quality observational studies yield a magnitude of effect similar to that of RCTs.[24–27] The main features of high-quality observational studies are the use of concurrent controls as opposed to historical controls, a prospective study design whenever possible, the selection of consecutive patients with clearly defined exclusion and inclusion criteria, the blinding of whoever can be blinded whenever possible—similar to RCTs (patient, investigator, outcome assessor, and data analyst), and a high follow-up rate. The balance of known prognostic factors can be achieved during treatment assignment and during study analysis by using techniques such as matching and stratification, which will adjust for differences in baseline characteristics. However, randomization remains the only method capable of achieving balance between unknown prognostic factors.

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Study Guide Questions

CHAPTER 4

1. Which of the following ultrasound probes would be most appropriate to image the kidney of a large 14-year-old boy?
   a. 3 mHz
   b. 5 mHz
   c. 7.5 mHz
   d. 10 mHz
   e. Any of the above
   Answer: a. The lower the millihertz of the probe, the better the tissue penetrance that is obtained. In order to image the kidneys in a large 14-year-old, the 3 Mhz probe offers the best tissue penetrance and would be the best choice.
2. An 18-month-old child is seen in the office for an IOUS. During the exam, an overlying rib obscures the child's left kidney and she becomes increasingly agitated and uncooperative. Which of the following positions is optimal to obtain an image of this kidney?
   a. Supine with the probe placed laterally along the axillary line
   b. Left lateral decubitus position
   c. Prone position
   d. The caretaker holding the child and imaging the kidney from the prone position
   e. Supine with the probe anteriorly in an intercostal space
   Answer: d. The prone position is the best position to image a kidney obscured by ribs. In an uncooperative younger child, the comfort of being held by the caregiver will often calm the child down and allow a better exam.
3. A 7-year-old girl is referred to the office for unilateral Grade 1 hydronephrosis. An IOUS is performed that confirms the finding of right hydronephrosis. All the following maneuvers on IOUS would help make the diagnosis of VUR *except* which?
   a. Imaging of the bladder transversely while full
   b. Imaging of the bladder transversely after voiding
   c. Imaging of the bladder parasagittally from the right
   d. Imaging of the bladder parasagittally from the left
   e. Imaging of the kidneys after voiding
   Answer: c. Use of IOUS is helpful in certain situations to delineate unilateral hydronephrosis due to VUR from UPJO. Resolution of hydronephrosis after voiding would favor a diagnosis of VUR, while persistence of unilateral hydronephrosis after voiding would suggest possible UPJO. Likewise, imaging for dilated distal ureters with a full bladder and resolution after voiding would also be suggestive of VUR. This is best done either transversely (ureters located posterior to the bladder) or longitudinally by viewing the ureter from the contralateral parasagittal view of the bladder. Thus, left parasagittal views of the bladder would be used to image the right ureter.
4. A 2-month-old child is seen in the office for evaluation of severe unilateral hydronephrosis. You perform an IOUS. Which of the following findings would be suggestive of a severely obstructed UPJ rather than an MCDK?
   a. An echogenic contralateral kidney
   b. Contiguity of the dilated renal pelvis and dilated calyces
   c. Involution of the kidney on serial follow-up exams
   d. Elongated kidney without reniform shape with multiple cysts
   e. All the above
   Answer: b. The differentiation between a severely obstructed kidney and an MCDK can be challenging. The key differential feature is the contiguity of the dilated renal pelvis with the dilated calyces that is not seen in an MCDK and the lack of involution of the severely obstructed kidney on serial exams. Furthermore, additional features suggestive of an MCDK include an echogenic elongated kidney without reniform shape, multiple noncommunicating cysts, a contralateral echogenic kidney, and perhaps most importantly, involution of the MCDK over time.
5. An IOUS is performed on routine follow-up on a 14-day-old neonate found to have bilateral prenatal hydronephrosis. Examination of the bladder ultrasound demonstrates echogenic material within the bladder lumen. Which of the following is most likely responsible for this finding?
   a. Bladder calculi
   b. Phosphate crystals
   c. Uric acid crystals
   d. Tamm–Horsfall protein
   e. Hypercalcuria
   Answer: d. The echogenic characteristics of a neonate's bladder are usually due to the Tamm–Horsfall protein. The normal urine in older children is echolucent.
6. A 6-year-old girl is seen in the office for evaluation of incontinence and recurrent UTIs. An IOUS is performed and a bladder capacity is calculated. What is the expected bladder capacity of a 6-year-old?
   a. 140 mL
   b. 180 mL
   c. 240 mL
   d. 280 mL
   e. 340 mL
   Answer: c. The formula to estimate the bladder capacity is as follows: Bladder capacity (oz.) = Age (years) + 2. To convert ounces to milliliters, one multiples the

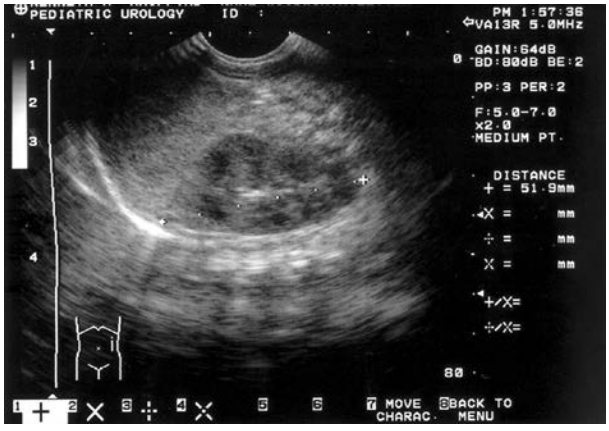
capacity by 30. Thus, a 6-year-old child should have a bladder capacity of 240 mL (or 8 oz.).

7. The following ultrasound is obtained on a 2-week-old neonate as follow-up for prenatally detected right hydronephrosis. Which of the following is the likely diagnosis?

a. Normal right kidney without hydronephrosis
b. Right kidney with SFU Grade 2 hydronephrosis
c. Right kidney with SFU Grade 4 hydronephrosis
d. Right kidney with duplex system and hydronephrosis of upper-pole moiety
e. Right kidney with duplex system and hydronephrosis of lower-pole moiety

Answer: d. This ultrasound image obtained in the office represents an ideal way to follow up on prenatally detected hydronephrosis. This kidney likely has a duplex system, as evidenced by separation of the central echogenic complex (CEC). The upper pole in a duplex system is seen laterally on a sagittal view of the kidney and the lower pole medially. In this case, hydronephrosis is seen in the upper-pole moiety.

8. An IOUS is obtained in the office on a 1-month-old as follow-up for prenatally detected hydronephrosis. The following ultrasound is obtained. What best describes the ultrasound finding?



a. Normal kidney
b. SFU Grade 1 hydronephrosis
c. SFU Grade 2 hydronephrosis
d. SFU Grade 3 hydronephrosis
e. SFU Grade 4 hydronephrosis

Answer: a. This is an image of a normal right kidney. The hypoechoic pockets seen between the renal cortex and renal sinus are prominent renal pyramids typically seen in children. These are not to be confused with hydronephrosis, as there appears to be no connection with the renal pelvis. Furthermore, there is no evidence of dilation within the CEC.

CHAPTER 10

1. Whitish discharge from a newborn girl's vagina is due to
   a. Yeast infection
   b. Strep vaginitis
   c. Maternal estrogens
   d. Ureteral ectopia
   e. Vaginal duplication

   Answer: c
2. The most common cause of paraphimosis is
   a. Chemical irritation
   b. Foreskin retraction without replacement
   c. Yeast infection
   d. Bacterial infection
   e. Diabetes

   Answer: b
3. Meatal stenosis is best diagnosed in the office by
   a. Physical exam
   b. History of voiding problems
   c. VCUG
   d. Observation of urinary stream
   e. Urethral calibration

   Answer: d
4. Urethral prolapse
   a. Usually requires surgery
   b. Occurs more commonly in African American girls
   c. Obstructs bladder outflow
   d. Often recurs
   e. Responds to antibiotics

   Answer: b
5. Labial adhesions
   a. Usually resolve spontaneously
   b. Should usually be separated
   c. Are caused by yeast infections
   d. Are commonly associated with vaginitis
   e. Respond to steroid ointments

   Answer: a
6. Phimosis after a neonatal circumcision
   a. Occurs after circumcision bleeding
   b. Should have the narrowed ring expanded with a hemostat
   c. Is caused by postcircumcision infection
   d. Is often solved by steroid ointment
   e. Is caused by leaving excess inner foreskin

   Answer: e
7. For physiologic foreskin adhesions,
   a. Separation in the office is recommended
   b. 90% of 2-year-old boys' foreskins should be retractable
   c. Smegma buildup leads to infections
   d. Circumcision should follow the first episode of balanitis
   e. Steroid ointment can separate ≥75%

   Answer: e

CHAPTER 13

1. In relation to fertility in the exstrophy male, which of the following statements is true?
   a. Ejaculation is commonly normal.
   b. The bulbocavernosus muscle is normal.
   c. The penile corpora tend to have a narrower girth than in "normal" men.
   d. The testes are structurally normal.
   e. Assisted fertility is always required.

   Answer: d. Typically, men with bladder exstrophy have poor ejaculation; one of the reasons behind this is the absence of a bulbocavernosus muscle. The penile corpora tend to be shorter but broader (wider girth) than normal. Many men do achieve fertility without assistance, but some will need support.
2. In surgery for DSDs, which of the following statements is true?
   a. The clitoral neurovascular bundle is classically ventral.
   b. Genital sensation may be affected.
   c. Intestinal vaginoplasty remains the first choice for reconstruction.
   d. Gonads should always be preserved.
   e. Surgery should be undertaken in early puberty.

   Answer: b. The clitoral neurovascular bundle is dorsal. Intestinal vaginoplasty is major complex reconstructive surgery, and other options should be explored and discussed. Many patients do well with dilation (especially in the absence of previous surgical scarring). The risk of preserving gonads is difficult to quantify. Gonads containing Y chromosomal material in a female phenotype are generally removed for fear of malignant change. The risk varies with diagnosis (e.g., mixed gonadal dysgenesis up to 50% to complete androgen insensitivity). Unless there is an obstruction causing pain and preventing menstruation, once a child has reached puberty, surgery should be deferred, if possible, until sexual activity is contemplated.
3. Which of the following is true regarding a diagnosis of posterior urethral valves?
   a. It is commonly associated with primary vesicoureteric reflux.
   b. It rarely has issues with fertility.
   c. It may be associated with Potter's facies.
   d. Early antenatal diagnosis confers a good prognosis.
   e. Bladder function normally stabilizes in early childhood.

   Answer: c. The vesicoureteric reflux is secondary to obstruction. These men commonly have issues with fertility; this may be due to poor ejaculation or alkalinized or abnormally aggluted semen. As a general rule, earlier diagnosis correlates with worse obstruction, and therefore is associated with a poor outcome. Bladder function may continue to deteriorate well into adult life.
4. In the follow-up of cystoplasty patients, which of the following statements is true?
   a. Bladder stones can be prevented with Mitrofanoff drainage.
   b. Annual cystoscopy is recommended for all.
   c. Subclinical metabolic acidosis should always be treated.
   d. Hematuria can be safely dismissed as catheter trauma.
   e. Gastrocystoplasty has a higher malignant risk than other bowel segments.

   Answer: e. The risk of bladder stones appears to increase with drainage through a Mitrofanoff channel—the theory being that dependent drainage is more effective at clearing mucus and debris. Annual cystoscopy is a poor screening method, but prompt and thorough investigation (including a cystoscopy) of symptoms (e.g., hematuria, pain, and unusual UTIs) is appropriate. Metabolic acidosis needs to be monitored if the bicarbonate is the only derangement and is mild; then no treatment is needed. However, if the chloride is high or there is any sign of symptoms, replacement is indicated.

CHAPTER 14

1. All the following conditions are felt to have a genetic predisposition *except*
   a. Wilms' tumor
   b. Vesicoureteral reflux
   c. Adrenogenital syndrome
   d. Ureteral duplication
   e. Bicornuate uterus

   Answer: e. Bicornuate uterus

CHAPTER 15

1. Adrenal cortical development in human embryogenesis is noted by the eighth week of gestation and is comprised of which of the following?
   a. Fetal zone, zona glomerulosa, and zona fasciculata
   b. Primitive zona glomerulosa, fasciculata, and reticularis
   c. Fetal zone and adrenal cortical cells
   d. Primitive neural crest cells interspersed with primitive adrenocortical cells

   Answer: c. Fetal zone and adrenal cortical cells

CHAPTER 17

1. In hereditary syndromes, which statement is not true?
   a. MEN type 1 is connected with inactivation of a gene on chromosome 11q.
   b. Li–Faumeni syndrome is related to inactivating mutations of TP53.
   c. ACC is linked with abnormalities in 11p15.
   d. Beckwith–Wiedemann syndrome is associated with the WT1 gene.

   Answer: d. Beckwith–Wiedemann is associated with the WT2 gene, abnormalities in 11q15. It is linked with Wilms' tumor, neuroblastoma, hepatoblastoma, and macroglossia.
2. Unilateral APAs do which of the following?
   a. Occur with increased frequency in girls
   b. Occur with equal rates between boys and girls

c. Tend to occur in older children
d. Occur with more frequency in boys

Answer: a. Although uncommon, unilateral APAs have been described in children as young as 3.5 years and affect girls more frequently than boys.

3. All the statements regarding primary hyperaldosteronism are correct *except* which of the following?
   a. Patients present with hypertension and/or hypokalemia, whereas those with secondary hyperaldosteronism do not.
   b. It will lead to a state of excess mineralocorticoid with high PRA.
   c. It may be caused by APA, idiopathic bilateral hyperplasia, or GRA.
   d. Adrenicortical hyperplasia is the most common cause in children.

   Answer: b. Primary aldosteronism will lead to a state of mineralocorticoid excess with *low* PRA.
4. In virilizing tumors, virilization is due to hypersecretion of adrenal androgens, including all *except* which of the following?
   a. DHEAS
   b. DHEA
   c. 11-Deoxycortisol
   d. Δ5-Androstenediol
   e. Δ4-Androstenedione

   Answer: c. Virilization is due to hypersecretion of adrenal androgens, including DHEA and DHEAS, Δ5-androstenediol, and Δ4-androstenedione, all of which may be converted to testosterone and 5α-dihydrotestosterone.
5. All the following conditions are associated with increased plasma catecholamine levels *except*
   a. Neuroblastoma
   b. Pheochromocytoma
   c. Hepatoblastoma
   d. Fever
   e. Stress
   f. Eating

   Answer: c. Norepinephrine and epinephrine are not specific to pheochromocytomas, as they are produced by the sympathoneuronal and sympathomedullary systems. Increased plasma catecholamine levels may be produced by a variety of conditions, including emotional stress, physical activity, eating, fever, and tumor secretion from pheochromocytomas and neuroblastomas.
6. The best investigation for pheochromocytomas is
   a. MIBG
   b. CT
   c. MRI
   d. Ultrasound

   Answer: a. Pheochromocytomas can be imaged with CT, MRI after ^{131}I- or ^{123}I-labeled MIBG. If an initial abdominal CT or MRI is positive, whole-body MIBG should be performed to confirm the diagnosis.

CHAPTER 20

1. There are three sets of kidneys that develop in mammals during embryogenesis. Which of these primitive kidneys do not function during development?
   a. Pronephros
   b. Mesonephros
   c. Metanephric mass
   d. None of the above
   e. All the above

   Answer: a
2. ARPKD is a rare inherited disorder with the abnormal renal configuration due to which of the following?
   a. Abnormal branching of the collecting duct and cyst formation in other parts of the renal tubules
   b. Abnormal formation of the distal convoluted tubule
   c. Enlargement of the collecting ducts
   d. Early obstruction of the tubules from ureteral obstruction potassium administration

   Answer: a

CHAPTER 30

1. The evaluation to define whether a UPJ obstruction exists has included all *except* which of the following studies?
   a. Intravenous pyelogram
   b. MAG-3 lasix renogram
   c. Renal and bladder ultrasound with resistive indices
   d. Antegrade perfusion study (Whitaker)
   e. MR urography with gadolinium

   Answer: c. Although there is not a gold standard that is agreed on in which to define a UPJ obstruction, all the above studies except a renal and bladder ultrasound provide some degree of functional assessment of the kidney. An ultrasound report should not state that the findings are consistent with a UPJ obstruction, but should report the degree of pelvicaliectasis that is present within a kidney.
2. Which surgical repair is most likely to succeed if there is a long segment of ureteral stenosis?
   a. Dismembered pyeloplasty
   b. Endopyelotomy
   c. Laparoscopic Anderson–Hynes pyeloplasty
   d. Spiral flap (Culp–DeWeerd) pyeloplasty
   e. Davis intubated ureterectomy

   Answer: d. Culp and DeWeerd's spiral flap is created from the redundant renal pelvis, transposed inferiorly, and then used to repair the defect at the UPJ. Such a flap is able to bridge the gap between the pelvis and healthy ureter over a distance of several centimeters.
3. Key steps in performing a dismembered pyeloplasty include all *except* which of the following?
   a. Placing a Penrose drain adjacent to the repair
   b. Excising as much redundant pelvis as possible
   c. Placing a feeding tube into the ureter during the suturing of the anastomosis
   d. Ensuring that a tension-free anastomosis exists
   e. Spatulating the ureter on the lateral margin at an adequate distance

   Answer: b. There is no clinical evidence that excessive reduction of the redundant pelvis is required to ensure a patent repair after pyeloplasty. The proximal ureter should be affixed to the most dependent portion of the renal pelvis, which then obviates concerns regarding redundancy.
4. Surgical options in the repair of a failed pyeloplasty include all *except* which of the following?

a. Endopyelotomy
b. Redo pyeloplasty
c. Transureteroureterostomy
d. Nephrectomy
e. Ureterocalicostomy

Answer: c. Depending on the clinical scenario, the presence of a missed crossing vessel, the functional status of the affected kidney, and the degree of hydronephrosis, each of the options above may be considered except transureteroureterostomy. That option is not appropriate due to the proximal ureteral location of stenosis.

5. Endopyelotomy is associated with the greatest likelihood for success in all *except* which of the following scenarios?
   a. Lack of a lower-pole crossing renal vessel
   b. Preserved renal function in the affected kidney
   c. Mild to moderate hydronephrosis
   d. Case of failed previous pyeloplasty
   e. Primary treatment for UPJ obstruction

   Answer: d. Endopyelotomy carries a long-term success rate, as high as 94%, as a secondary treatment for UPJ obstruction after previously failed pyeloplasty. Decreased renal function, severe hydronephrosis, and a lower-pole crossing vessel are known to decrease the likelihood of success in primary treatment cases.
6. Which of the following is an advantage gained with robotic assistance compared with pure laparoscopy?
   a. Two-dimensional visualization in high definition
   b. Ability to perform laparoscopic surgery via a camera port and a single additional port
   c. Dampening of tremor
   d. Decreased analgesia requirement in the postoperative period
   e. Shorter length of postoperative hospitalization

   Answer: c. The clear advantages of robotic-assisted laparoscopy over traditional laparoscopy include three-dimensional visualization (now in high definition), articulating instruments with greater degrees of freedom, and dampening of tremor. No comparable difference has been demonstrated in any postoperative parameters.
7. Appropriate postnatal radiographic imaging of an infant with prenatally detected MCDK has included all *except* which of the following studies?
   a. Voiding cystourethrography
   b. Renal and bladder ultrasound
   c. MAG-3 lasix renogram
   d. Dimercaptosuccinic acid (DMSA) renal scan
   e. MR urography

   Answer: e. In the past, it was important to identify those patients with reflux who had a solitary functioning kidney. An ultrasound has been the predominant modality to define an MCDK, and either a MAG-3 lasix renogram or a DMSA scan will demonstrate no uptake in the MCDK. There is no role for MR urography in this situation to characterize an MCDK.

CHAPTER 34

1. Following blunt abdominal trauma, patients presenting with a history of hematuria disproportionate to the severity of trauma are most likely to have a
   a. Renal tumor
   b. Renal lithiasis
   c. Myoglobinuria
   d. Congenital anomaly
   e. Immature thoracic cage

   Answer: d
2. Delayed hemorrhage occurring 2 weeks following a grade 3 renal fracture should be managed by repeat CT scan and
   a. Observation
   b. Cystoscopy
   c. Epsilon aminocaproic acid (Amicar)
   d. Angiography with selective angiographic embolization
   e. Renal exploration

   Answer: d
3. Three days after selective embolization of a segmental renal artery for persistent bleeding following a grade 4 renal fracture, the patient has a persistent ileus, fever of 40°C, and continued left flank pain. He is currently on broad-spectrum antibiotics. Physical examination reveals no signs of peritoneal localization. The next step is to obtain blood and urine cultures and
   a. Continue observation
   b. Change antibiotics
   c. Obtain a repeat CT scan
   d. Perform aspiration and culture of perinephric hematoma or urinoma
   e. Perform an exploratory laparotomy

   Answer: a
4. A 6-year-old boy has persistent hypertension 12 weeks following a grade 4 left renal fracture. CT angiography reveals a left upper-pole AV fistula with complete resolution of the previous existing left perinephric hematoma and urinoma. Extensive subcapsular fibrosis has developed surrounding the entire left kidney. The right kidney is within normal limits. A DMSA scan reveals 30% differential function of the left kidney and 70% differential function of the right kidney. The serum creatinine and renal clearance are normal. The next step is to continue antihypertensive medications and
   a. Observe
   b. Obtain selective renal vein renins from the upper- and lower-pole vessels of the left kidney
   c. Perform angioinfarction of the left upper-pole AV fistula
   d. Perform a left upper-pole partial nephrectomy and decortication of the perinephric fibrosis
   e. Perform a left nephrectomy

   Answer: c
5. A 15-year-old boy presents with a 22-caliber gunshot wound to the left flank. Evaluation reveals an entrance wound posterior to the left anterior axillary line; no exit wound is seen. Vital signs are stable, and the patient has no signs of peritoneal irritation. A CT scan reveals a grade 2 left renal injury. The right kidney is within normal limits. No air is noted in the peritoneal cavity, and no associated organ injuries are noted. The distal ureters are intact bilaterally. Your next step is to initiate intravenous antibiotics and
   a. Observation
   b. Intravenous indigo carmine and local exploration of the wound

c. Exploratory laparatomy alone
d. Retroperitoneal exploration and renorrhaphy alone
e. Exploratory laparatomy, retroperitoneal exploration, and renorrhaphy

Answer: a

6. A 4-year-old girl presents with a grade 3 renal injury following blunt renal trauma. A CT scan reveals a large perinephric urinoma, no devitalized renal fragments, and distal ureters intact bilaterally. There are no associated intra-abdominal injuries. The next step is admission to the hospital and
   a. Observation
   b. Cystoscopy and placement of a double-J stent
   c. Percutanous nephrostomy
   d. Percutanous tube placement into the urinoma
   e. Exploratory laparatomy

   Answer: a
7. A 12-year-old boy with a history of a pedestrian motor vehicle accident 2 hours ago is clinically stable. A triphasic CT evaluation reveals a grade 3 left renal fracture with a 2 cm devitalized left lower-pole fragment. Extravasation of contrast is seen lateral to the left kidney. No distal left ureter is visible. The right kidney is within normal limits. The right distal ureter is visible. No other intra-abdominal injuries are noted. The next step is
   a. Observation
   b. Exploratory laparatomy
   c. Cystoscopy and retrograde pyelogram
   d. Percutaneous drainage of the urinoma
   e. Percutanous nephrostomy tube placement

   Answer: c
8. A 3-year-old girl sustained an isolated grade 4 left renal trauma following a high-speed motor vehicle accident. The initial CT scan and a CT scan 3 days posttrauma revealed a large left urinoma with a left upper-pole fragment widely separated from the kidney contrast seen in the distal left ureter. The right kidney is normal. Do to persistent ileus, the patient undergoes placement of a 5 French double-J stent on the third posttraumatic day. Six days posttrauma the patient has continued ileus and left flank pain. A CT scan reveals persistent urinoma. The next step is
   a. Cystoscopy and placement of an 8 French double-J stent
   b. Placement of a percutanous drain into the urinoma
   c. Placement of a percutanous nephrostomy tube
   d. Angiography and angioinfarction of the left upper pole
   e. Retroperitoneal exploration and renorrhaphy

   Answer: c

CHAPTER 36

1. Which of the following are involved in the outgrowth of the ureteral bud?
   a. GDNF
   b. Renin–angiotensin system
   c. PAX2
   d. Sonic hedgehog
   e. All the above

   Answer: a, b, c

CHAPTER 38

1. Ureteral triplication
   a. Can be easily diagnosed prenatally
   b. Is associated with a pathognomonic constellation of symptoms
   c. Usually mandates urgent lower urinary tract reconstruction
   d. Is bilateral in most cases
   e. Is often associated with other systemic or urologic anomalies

   Answer: e
2. Which of the following midureteral surgical techniques is most likely to result in ureteral stricture?
   a. Renal mobilization
   b. Ureteral stent
   c. Removal of periureteral adventitia
   d. Perianastomotic drains
   e. Spatulation of both proximal and distal ureteral segments

   Answer: c
3. Retrocaval ureter is most often associated with
   a. Persistence of the supracardinal vein
   b. Situs inversus
   c. Hematuria
   d. The left ureter
   e. Medial ureteral deviation

   Answer: e

CHAPTER 44

1. The most important surgical goal of ureteral reimplantation is the reestablishment of a flap valve mechanism that requires a ratio of ureteral tunnel length to ureteral diameter of
   a. 3:1
   b. 5:1
   c. 10:1
   d. 1:1
   e. 2:1

   Answer: b
2. During the modified Politano–Leadbetter repair, where is the new ureteral hiatus placed in relation to the original hiatus?
   a. Inferior and medial
   b. Superior
   c. Lateral
   d. Superior and medial
   e. Medial

   Answer: d
3. The appropriate evaluation and treatment of asymptomatic hydronephrosis present after open ureteral reimplantation includes
   a. Diuretic renography and ureteral stent placement
   b. Ureteral stent placement
   c. Percutaneous nephrostomy placement
   d. Observation
   e. Repeat reimplantation

   Answer: d
4. The major drawback to the cross-trigonal reimplantation technique is

a. Frequent stenosis of the ureteral orifice
b. Excessive "kinking" of the ureter after repair
c. Insufficient muscular backing
d. Difficulty in accessing the ureter during endoscopy
e. Increased chance of ureteral devascularization
Answer: d

5. Postoperative urinary retention most commonly occurs following which open technique?
a. Modified Politano–Leadbetter
b. Gil-Vernet
c. Lich–Gregoir
d. Glenn–Anderson
e. Cohen cross-trigonal
Answer: c

6. When choosing open repair techniques, which factor supports the use of the Glenn–Anderson approach?
a. Lateral displacement of the ureters
b. Stenotic ureteral orifices
c. Large, wide trigone
d. Numerous preoperative UTIs
e. Presence of bladder–bowel dysfunction
Answer: a

CHAPTER 49

1. The bladder develops from
a. The urogenital sinus
b. The mesoderm of the anterior abdominal wall
c. The endoderm
d. The ureteral buds
e. All the above

2. Place the following events in correct chronological order:
a. Pronephros involutes
b. Urorectal septum descends
c. Proximal urethra forms
d. Müllerian ducts form
e. Wolffian ducts form

1. a, b, c, d, e
2. a, b, e, c, d
3. a, b, c, e, d
4. a, d, c, b, e
5. a, e, b, c, d

CHAPTER 69

1. The fetal gonads begin to differentiate into either a testis or an ovary at approximately which week of gestation?
a. Week 3
b. Week 6
c. Week 9
d. Week 12
e. Week 15
Answer: b

2. Testicular descent from the abdominal cavity through the inguinal canal and into the scrotum may be influenced by all *except* which of the following?
a. Gubernacular guidance
b. Increased intra-abdominal pressure
c. Local hormonal factors
d. The processus vaginalis
e. Completed development of the vas deferens
Answer: e

3. Which of the following is a remnant of the Müllerian duct system?
a. Appendix testis
b. Epoopheron
c. Gartner's duct
d. b and e
e. All the above
Answer: a

CHAPTER 75

1. What hormone is most directly responsible for the development of the external male genitalia?
a. Testosterone
b. Estrogen
c. Mullerian inhibiting substance
d. Dihydrotestosterone
e. Growth hormone
Answer: d

2. The etiology of penile necrosis is likely which of the following?
a. Use of electrocautery with clamp devices
b. Use of electrocautery during freehand sleeve circumcision
c. Use of Dermabond and other skin glues for circumcision closure
d. Postcircumcision hematoma development
e. Local anesthetic use during circumcision
Answer: a

3. When considering a Nesbit placation, the anatomical location of the nerve fibers that course along the penis is which of the following?
a. Six o'clock
b. Three o'clock
c. Twelve o'clock
d. Nine o'clock
e. Two o'clock
Answer: c

4. What is considered an abnormal stretch penile length in a newborn?
a. Less than 1 cm
b. Less than 1.5 cm
c. Less than 2 cm
d. Less than 2.5 cm
e. No normal value exists
Answer: c

5. What is the recommended intial management of high-flow priapism in the pediatric population?
a. Angiographic embolization of arteriovenous fistulization
b. Observation and compression
c. Irrigation and injection of alpha-adrenergic agonists
d. Irrigation and injection of alpha-adrenergic antagonists
e. Winter's shunt
Answer: b

6. In patients with an ectopic scrotum, what additional testing should be performed?
   a. Renal ultrasound
   b. VCUG
   c. MRI abdomen and pelvis
   d. Serum testosterone
   e. Urinalysis
   Answer: a
7. In counseling adolescents about varicocele, which of the following statistics are correct regarding the incidence of varicocele in the population and the incidence of infertility in men who have varicocele:
   a. 50%:50%
   b. 40%:90%
   c. 40%:15%
   d. 40%:40%
   e. 15%:40%
   Answer: e
8. In determining the need for surgical intervention in an adolescent with varicocele, which of the following testicular size discrepancies has been traditionally used as an indicator for the need for varicocelectomy?
   a. 30%
   b. 40%
   c. 20%
   d. 15%
   e. 50%
   Answer: c
9. After varicocelectomy, what percentage of patients will experience testicular "catch-up growth"?
   a. 80%
   b. 20%
   c. 50%
   d. 100%
   e. 90%
   Answer: a
10. The predominant histopathological finding in adolescents undergoing varicocelectomy is which of the following?
   a. Sertoli cell hyperplasia
   b. Hyalinization of the testicle
   c. Leydig cell atrophy
   d. Leydig cell hypertrophy
   e. No abnormality
   Answer: c
11. How are neonatal/adolescent testicular torsion classified?
   a. Intravaginal/extravaginal
   b. Intravaginal/intravaginal
   c. Extravaginal/intravaginal
   d. Extravaginal/extravaginal
   e. Random pattern
   Answer: c
12. What is the embryological origin of the appendix testis?
   a. Wolffian duct remnant
   b. Mullerian duct remnant
   c. Ureteric bud remnant
   d. Gonadal ridge remnant
   e. Testicular remnant
   Answer: b
13. Bilateral abscence of the vas deferens can indicate which genetic condition?
   a. von Hippel–Lindau
   b. Fragile X syndrome
   c. Tuberous sclerosis
   d. Cystic fibrosis
   e. VACTERL
   Answer: d
14. Multiple epididymal cysts in a young male patient indicate the need for what other imaging study due to its possible association with a genetic condition?
   a. Spine MRI
   b. VCUG
   c. Renal ultrasound
   d. electroencephalogram (EEG)
   e. Dimercaptosuccinic acid scan
   Answer: c
15. Which of the following shunts for priapism has the highest risk of long-term erectile dysfunction?
   a. Winter's
   b. Ebbehoj
   c. Al-Ghorab
   d. Grayhack
   e. None of the above
   Answer: d

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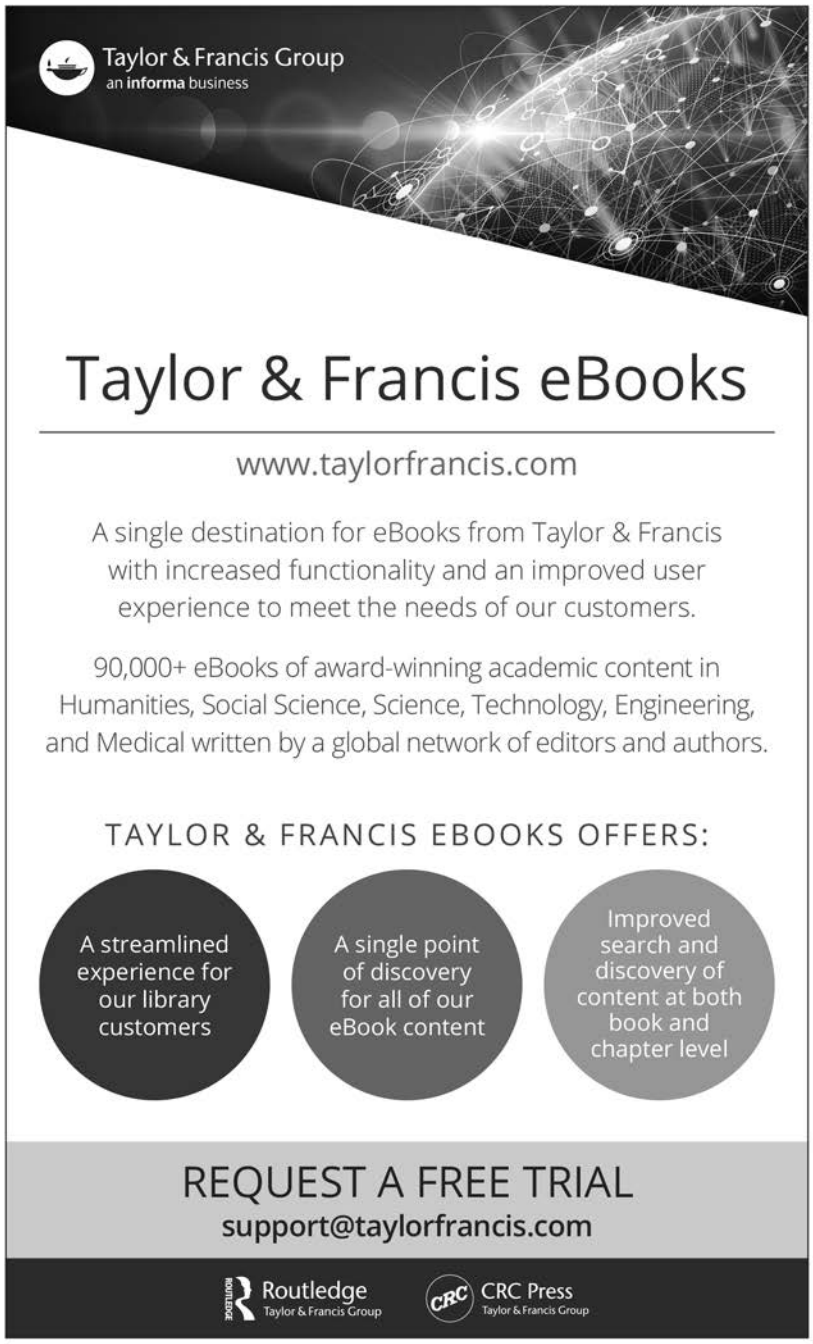
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